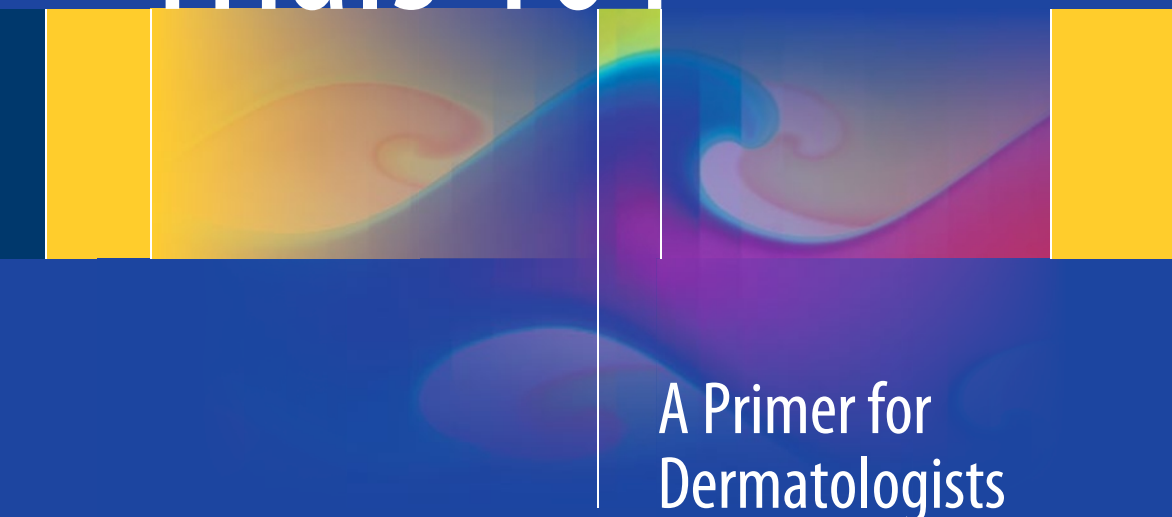
Adnan Nasir
Editor

Clinical Dermatology Trials 101



A Primer for Dermatologists

Springer

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For Angela, Sofia, and Julia

Preface

Introduction

Welcome to the arena of clinical investigation in dermatology. As a physician, you are in command of a variety of marketable tools, techniques, and skills. Whether you are in academic medicine, work in a multispecialty group, or are in a single-specialty dermatology practice, you might be interested in broadening your horizons by embarking on an adventure in clinical discovery. You may be interested in working on your own, or with others in the large and expanding opportunities in dermatology pharmaceutical and device research. This book is a comprehensive guide to taking your first steps in dermatology clinical trials.

The Benefits of Clinical Research

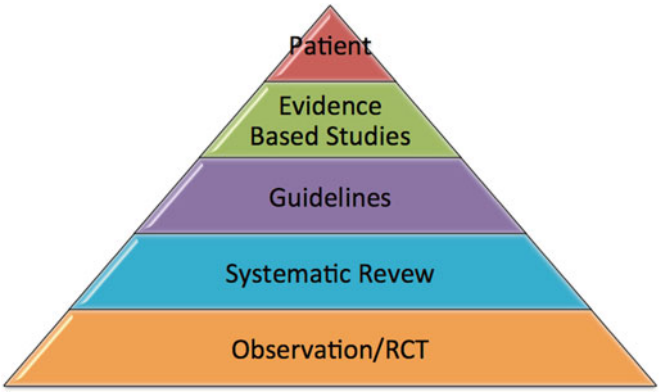
When you make the decision to conduct clinical trials, you will learn that it is something you can accomplish in a variety of ways. You may belong to a large academic medical center or university. Your department or institution may already have an affiliated investigative facility. There may be established dermatologists within the facility, or you may, as the only dermatologist, expand the scope of responsibility of the facility. You may be in solo private practice or part of a single- or multi-specialty clinical practice. Your location may not offer any clinical research at all, and you may be the first to set up and establish a niche in dermatology research among your immediate colleagues. You may be interested in a career in government, at a clinical trial unit at the National Institutes of Health. You may be interested in writing protocols and overseeing clinical research at a pharmaceutical company. Alternatively, you may be entrepreneurial and intend to set up your own company based on research you do.

Whatever route you take, and whatever the goals you wish you achieve, when you actively engage in a clinical research enterprise, you join a national and global com-

munity of driven and talented dermatologists who derive great pride, satisfaction, and intellectual stimulation from the work that they do. You will interact closely with scientists, technical experts, and a variety of staff in moving cutting-edge research forward in a standardized and safe manner. You will add to your knowledge of the basic biology of disease. You may sharpen your clinical skills by learning the latest advances and protocols. You will meet colleagues and make many friends in private practice, clinical research centers, academia, industry, finance, the media, and government. You may publish and present some of your findings and local, national, and international conferences. In addition to diversifying your revenue stream, you will diversify the treatment options you can offer patients and referring colleagues in your community. You may enjoy investigative dermatology so much that you may embrace it full time.

Bottlenecks in Drug and Device Development

Industry, the government, and your patients need you. The main reason is that development of drugs and devices is impeded by ever more and ever narrowing bottlenecks. These bottlenecks stem from competing priorities among regulators, drug and device developers, patients, the public, governments, investors, and society. Bottlenecks are costly and frustrating to developers and to patients. Patent clocks tick on every compound or device from the moment the patent is filed. The sooner a drug or device is approved, the longer a drug or device maker has patent exclusivity and the greater revenue the maker can recover to offset the costs of research and development. Tight bottlenecks mean long approval times, abbreviated patent exclusivity, and diminished revenue. Longer approval time may also give a rival a chance to create a competitive product, further eroding the value of a patented drug or device. Industry, shareholders, and impatient investors often exert pressure on business decisions and may terminate research on an otherwise promising breakthrough because of economic ramifications years down the road. Patients ultimately suffer. Benefits of new research getting from the bench to the bedside are delayed, or tabled.



Engaging in clinical research is all about the patient. Many years of effort from many quarters must converge to ultimately benefit patients. Observational studies and randomized controlled trials generate results which, in systematic reviews, lead to clinical guidelines. These are refined in key evidence based studies to become the latest standard of care.

The Investigator Shortage

Dermatology is suffering an acute shortage of clinician investigators. The timing could not be worse for industry or better for investigative dermatologists. Now that the pace breakthroughs are reaching an inflection point in a curve shooting upward, dermatologists are either not entering clinical research or not renewing their research contracts. New drugs and devices using advanced technology—including nanotechnology—are being discovered at a rapid rate and are languishing in a bottleneck between research (the preclinical research phases of drug discovery and animal studies) and development (clinical trials). The ampersand between R&D may as well be a bottleneck twisting itself into a pretzel.

Clinical trials are expensive, time-consuming, and absolutely essential to marketing approval of pharmaceuticals and devices. High quality investigators in dermatology are needed to gather the data necessary for submission to the FDA and other government bodies. Only a large cadre of capable, qualified, and enthusiastic dermatology investigators can increase the throughput of clinical trials, reduce costs, and speed the time to market breakthrough drugs and devices.

There are other reasons for drugs and devices not making it to consumers, but a principal one is investigator shortage. Training in medicine and board certification in dermatology are long, arduous processes. Debt obligations limit career choices. Additional training required for investigative dermatology may not appeal to everyone. The challenges and administrative burdens of conducting clinical trials are growing. Protocols are more complex. Regulations are more cumbersome. Some investigators only complete one trial in their lifetime, never bothering to seek additional studies. This shortage is felt so acutely in industry that at least one company (Galderma) has established an in-house investigative dermatology fellowship in order to train the next generation of clinical researchers. The National Institutes of Health has several programs to encourage young dermatologists to pursue a career in clinical research. There are several university-sponsored dermatology research training fellowships in the USA as well as online courses sponsored by academia (CITI) and the government (http://www.fda.gov/Training/default.htm). By becoming an investigative dermatologist, you will be a key contributor to the solution.

Tectonic Shifts in Research

There are many routes to becoming a clinician investigator. Even if you have not completed a government or industry-sponsored clinical research fellowship, or are not on faculty at a major academic medical center, you can still begin a successful career as an investigative dermatologist. In fact, for a number of reasons, there has been a shift to move clinical research out into the community. The preponderance of investigative dermatologists in the twenty-first century is now in private practice or directors of clinical research centers. This is true in the USA and globally, where more and more trials are conducted.

Good Clinical Practices

This book will go over what you need in order to establish yourself as an investigative dermatologist overseeing trials on human subjects. You will acquire the basic knowledge you need to conduct studies safely and in accordance with internationally recognized principles and practices. You will learn that clinical trials require sponsorship, whether from grants or contracts, whether from the government or industry. You will learn that sponsors will require you to have minimum qualifications as an investigator. One of the chief qualifications is a solid grasp of good clinical practices (GCP). GCP is not about taking care of dermatology patients. It's about adhering to universal practices for the protection of human subjects, for the collection of data, and for documentation of data in a format acceptable to government regulatory agencies for approval.

Regulatory Bodies

You will learn about the key players in regulation. The Food and Drug Administration (FDA) has three major sections which regulate innovations in dermatology. The Center for Drug Evaluation and Research (CDER) oversees drug developments. The Center for Biologic Evaluation and Research (CBER) oversees vaccines, therapeutic sera, toxins, antitoxins, blood and blood products, allergens, immunoglobulins, cytokines, and biotechnology-derived products such as cell-derived products or recombinant DNA-derived products. The Center for Devices and Radiological Health (CDRH) is responsible for ensuring the safety and effectiveness of medical devices and minimizing unnecessary exposure to radiation-emitting products. You will learn how these agencies oversee research and protect the public.

Practical Tips

You will learn about the history of clinical investigation. You will understand the regulations governing clinical research in that historical context. You will learn about the drug and device discovery process from initial idea to final approved product. You will learn about post-marketing surveillance to detect and measure unforeseen benefits and risks of approved products. You will also learn the nuts and bolts of running investigative sites. You will learn how to solicit sponsorship for ongoing or new trials. You will learn what qualities sponsors and granting agencies look for in order to consider you a potential investigator. You will learn what to look for when considering a potential sponsor or research project.

Contracts and Budgets

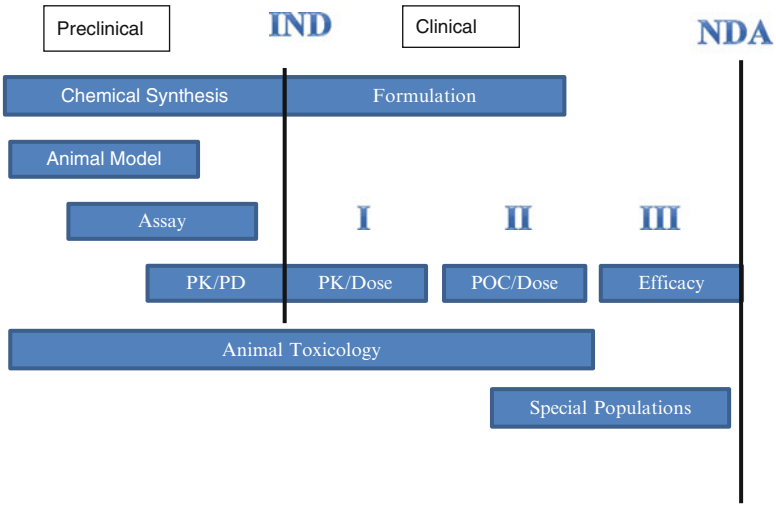
You will learn how to negotiate contracts and budgets. You will learn how to do a study feasibility analysis. You will learn how to spot studies that are right for you and how to say no to the ones that are not. You will learn about contract pitfalls such as publication embargoes and intellectual property. You will learn the practical details of implementing a study from standard operating procedures, managing study materials and documentation, recruiting and retaining volunteers, dealing with adverse events. You will be informed on regulations governing research that you do and the training requirements for you and your staff. You will learn about the hazards of Anti Kickback Statutes, Stark Laws, and privacy laws such as HIPAA. You will learn how to work with contract research organizations and site management organizations.

Perspective

You will learn about important ethical issues for you and various players in your research team. You will learn about vulnerable populations in clinical dermatology. You will gain an industry perspective on investigative dermatology. Finally, you will learn about opportunities for conducting clinical research in dermatology.

Welcome

If you are already part of an established research enterprise, once you have completed your training and certification, you will be ready to solicit or participate in trials. If you are setting up a new site, you will need to make your entity legal and compliant with regulations, assemble your team, and outfit your facility. Using the resources described in this book, you will be able to develop your network to become a sought-after investigator in dermatology clinical trials. You will be the first to glimpse treatments at the limits of science. Welcome to dermatology beyond the horizon.



From bench to bedside, drug and device development can take 10–15 years. The preclinical phase includes characterization of compounds and entities, the development of animal models and assays, animal toxicology studies, pharmacodynamics, and pharmacokinetic studies. Clinical trials in human subjects are the linchpin of the whole process.

Early Development: This is the preclinical in vitro, in vivo, or in silico phase. Once these studies are done, permission to test in humans is given by the FDA via the IND (Investigational New Drug) application. This application has an outline for the proposed studies. Once the application is filed, the clock starts ticking, as the patent is good for 20 years.

Phase I: 20–100 healthy volunteers are given increasing doses to test safety, tolerability, PK, and PD. The dose is 1/10th of the human equivalent dose where NOAEL (no adverse effect level) is seen in the most sensitive species in two different animal studies. During this phase, factors which affect absorption, metabolism, and excretion of the drug are evaluated. Microdosing or phase 0 trials can be substituted for this phase.

Phase II: In Phase II trials, the test agent is given to larger groups of people (200–300) to see if it is safe. This may also be the dose-finding phase. In Phase II trials, because there are larger groups of subjects, they may have varying degrees of illness and the variety of responses as well as a variety of toxicities can be observed in this phase. Sometimes comparison drugs or placebos are tested in this phase.

Phase III: Broadens the population receiving the drug, including more real-world subjects with other underlying illnesses. Sometimes the drug is tested against placebo. It is unethical and illegal to give a placebo to seriously ill patients if alternative therapies are available. Hence, these studies have comparator drugs. This phase,

which gathers more safety and dosing evidence, is required before submitting a New Drug Application (NDA). These trials often involve thousands of patients and are multicentered. At least two successful Phase III trials are required before FDA approval. This is less stringent for oncology, where one trial is required. Because this phase is so important to a medication's success, an independent DSMB (Data Safety Monitoring Board) is enlisted, especially if the study team's members are blinded, to alter the trial, or halt a trial because of safety concerns or because one group is doing substantially better than another.

Phase IV: Typically done for marketing purposes rather than intellectual curiosity. These trials compare an approved drug with a major competitor. This phase can also change a medication's status from prescription to OTC. It can also target genders, ages (pediatric population), and ethnicities.

Post-marketing surveillance can pick up unexpected serious side effects (thalidomide, Ketek), which can lead to withdrawal or additional warning labels. Some of these side effects and toxicities may go undetected because of small numbers (ICH requires approximately 1,500 subjects; most adverse events occur in the first 6 months, so you need 300–600 patients for that time to detect events at a frequency of 0.5–5 %; to detect AEs of 1 %, you need more than 100 patients for more than a year).

Chapel Hill, NC, USA Adnan Nasir

Acknowledgments

Clinical research is a collaborative venture, and this project is one that could not have been accomplished without the devotion and dedication of a number of individuals. I would like to thank Maria Smilios, Springer's sharp-eyed and masterful development editor. She has worked tirelessly to bring this project together. From fielding numerous queries from me and other contributors, to early morning phone conferences and late night emails, she has ushered the manuscript forward with tractor beam focus, wry wit, and vim. Throughout the development process, I have become convinced that either she does not sleep or has a nocturnally active twin. Rebekah Amos has had the vision to foresee the central role of clinical research in the future of dermatology and took on this endeavor, providing guidance, support, and careful forethought in the development of this text. Her integrity, wisdom, and allegiance have made her a pole star in publishing. I am truly grateful for her efforts on my behalf and on behalf of advancing dermatology and medicine. Many of the lessons I have learned have been gleaned from or germinated under the tutelage of my mentors. I thank Dr. Anthony Gaspari, who graciously offered me the chance to work with him on basic mechanisms of immunity in the skin. Two decades later, the same molecules and pathways we studied in proto-embryonic preclinical stages have led to immune-based therapies of autoimmune skin diseases and broad spectrum of malignancies, including melanoma. Two decades later, he has remained a true mentor, colleague, and friend. I would like to thank Dr. H. Mendall Jordan for getting me started in clinical dermatology and clinical research. He has been a friend, guide, and colleague in all of the important medical decisions I have made over the past 15 years. I am deeply thankful to colleagues and co-investigators at our multidisciplinary clinical research institute including Drs. Angela Hodge, Miroslav Gavazov, Anne Tuveson, Tamara Housman, Ella Grach, Charles Barish, Douglas Holmes, Treva Tyson, Jonathan Flescher, Arvind Jariwala, Wayne Harper, Bulent Ender, Singar Jagdeesan, Susan Eder, Mary Ann Pollock, and Christopher Daniels who have taught me about more than good clinical practices and protocols. They have shared with me their collegiality, their compassion, and their profound devotion to

the sanctity and dignity of human beings. I would like to thank Marion Peoples—chief coordinator of all studies and trials at the research institute and uber problem solver—for her bright spirits, unerschutterlichkeit, and gleichmutkeit. Without her, all our work would be kaput. I am also profoundly grateful to the many hundreds of patients and families who have done so much to further medicine and science in the name of clinical research. They are the quiet, towering heroes on whose shoulders all of medical knowledge stands. Finally, I would like to thank my family for their support, patience, and tolerance of intrusions on our limited time together.

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Chapter 1
History and Background

Adnan Nasir

We choose to go to the moon. We choose to go to the moon… (interrupted by applause) we choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win, and the others, too.

John F. Kennedy, Jr.
12 September 1962
Rice University

1.1 Ancient Origins

Clinical trials have an ancient and multifarious history. Some of the earliest descriptions are separated by only a few centuries but nearly six thousands of miles. Many of these trials were observational, involving case studies to develop a body of medical knowledge. They have evolved over nearly five millennia into the complex enterprise of the modern era (Fig. 1.1).

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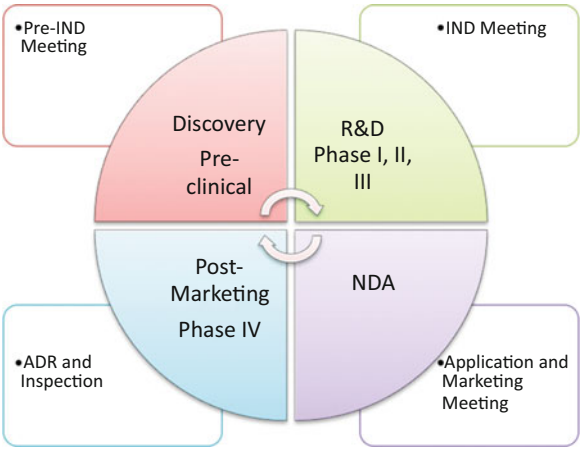


Fig. 1.1 Medication research involves a "Life Cycle" which starts with observation of a clinical or basic science phenomenon. The observation leads to testable hypotheses, which point the way to a biological mechanism of disease. Confirmed hypotheses lead to potential diagnostic tools or therapies which are further tested and refined in preclinical and clinical phases. In the post-marketing phase, feedback from the "real world" of the clinic generates new observations, which lead to further testable hypotheses, and the cycle continues. Thus clinical research begins and ends with humans in our environment

1.2 Imhotep

Imhotep lived around 3000 BC. A polymath, Imhotep was an astronomer, conjurer, priest, architect, dentist, surgeon, and pharmacobotanist. While debated, he is believed to be the author of the Edwin Smith Papyrus. In it, there are 48 detailed clinical case studies, demarcated by organ system. The case reports are written like modern day SOAP notes. Each case is given a title, which suggests the presenting nature of the problem. The title is followed by an inspection and examination of the patient. This is followed by a diagnosis, prognosis, and treatment plan. The case studies provide detailed knowledge of organ function. It contains the first written reference to the brain. The relationship of brain and spinal injuries to paralysis are described, such as an understanding that crush injuries of the spine affect the body differently at each spinal level. The depth of medical knowledge and physiology in the papyrus suggested a sophistication that exceeded Hippocrates and preceded him by nearly 2500 years.

1.3 Shen Nong

Shen Nong (神農, literally "divine farmer") was a legendary Chinese Emperor who lived around 2700 BC. He is believed to be the author of the Shen Nong Ben Cao Jing (神農本草經) a book on medicinal plants and tea [1, 2]. It consists of three

volumes. The first describes the beneficial effects of nontoxic stimulants such as ginseng, orange, and cinnamon. The second volume covers extracts used to treat human disease such as cucumber and ginger. These are listed as mildly toxic. The third volume catalogs toxic substances such as those derived from peach pits and rhubarb.

1.4 Hippocrates

Hippocrates of Kos (400 BC) promoted medical ethics and professionalism through his Oath [3]. He was a proponent of natural (as opposed to supernatural or divine) causes of disease. He developed a theory of medicine that disease was not a punishment for sin but caused by environmental factors or lifestyle. He contributed 42 case reports to the medical literature. He described dermatologic phenomena such as clubbing. He was the first to use the Greek word *Karkinos* to describe the crab-like extensions of blood vessels to a central bulbous tumor mass.

1.5 Sushutra

A near contemporary of Hippocrates, Sushruta (600 BC) of Varanasi wrote a surgical text, the Sushruta Samhita (सुश्रुतसंहिता), which described detailed skin surgery, plastic surgery, and reconstructive surgery including rotation flaps and pedicle flaps. To maximize training and minimize harm to patients Sushruta Samhita outlines meticulous practice of procedures on vegetables, plants, bamboo, animal skin, and dead animals.

1.6 Galen

Galen (Γαληνός, meaning "calm") of Pergamon (150 BC), a patrician's son, was a philosopher and physician to emperors Marcus Aurelius, Commodus, and Septimius Severus [4]. One of the most prolific authors of medicine and philosophy in ancient Greece, he is believed to have written or dictated nearly ten million words, a third of which survive. He has written major texts on physiology, anatomy, pharmacology, and diseases. He described several important diseases, such as the Antonine Plague (likely smallpox). He conducted animal experiments to understand human disease. He performed dissections on living and dead animals. He studied the four humors (blood, phlegm, yellow bile, and black bile) of Hippocrates' time. In animal studies, he made the distinction between venous (dark red) and arterial (bright red) circulation. In a form of Imhotep redux, he transected the spinal cords of animals to show paralysis and inferred his findings applied to human disease.

1.7 The Middle Ages

Many of the Galenic texts were translated into Arabic and contributed to the rise of Islamic medicine during the Dark Ages and early Middle Ages. During this period, pharmaceuticals such as opiates were commonly found along trade routes. Animal studies were done. The beginnings of the understanding of anatomy and physiology were developed through animal studies and ultimately work on human cadavers. Theories of disease went from supernatural to natural. Experiments done on human subjects involved controls. The concept of consent was developed.

1.8 Avicenna

Avicenna (سينا بن) of Bukhara (1000 AD) wrote the Canon of Medicine (القانون في الطب) In it, he expands on the work of Galen and describes investigational pharmaceutical principles which hold to this day, including use of pure drug, dose escalation, control groups, reproducibility, confirmation of animal tests in human subjects, and long-term observation [5].

1.9 Circulation

In the seventeenth century, blood and the circulation became better understood, through the work of William Harvey—who described circulation through the heart, lungs, body, and back—and Richard Lower and Edmund King who performed early blood transfusions. In Galen's time, the blood was believed to go from the left side of the heart to the right through small pores or perforations in the septum. Harvey and his contemporaries were able to show the pulmonary circulation as the bridge between the right and left ventricles.

1.10 Scurvy

James Lind, 1747 AD, developed the concept of a control group. He performed a study of scurvy, dividing 12 sailors into 6 groups of pairs [6]. The pairs who were given cider, seawater, vinegar, sulfuric acid, or a mixture of nutmeg/garlic/horseradish did not improve. Only the group given one lemon daily improved. Scholars have since critiqued the lack of informed consent in Lind's study.

1.11 Communicable Disease

In the 1700s, Edward Jenner developed a method for smallpox vaccination [7, 8]. Vaccination played an important role in the protection of George Washington's troops during the Revolutionary War. Laws were passed to ensure the purity of vaccines and the qualifications of those administering vaccines [8–10].

In the eighteenth century, a case in which two surgeons disunited a partially healed fracture, lead to one of the early requirements for informed consent (1767, Slater vs. Baker & Stapleton). John Snow, an anesthesiologist, showed cholera was spread by the water supply, and is credited with founding epidemiology as a discipline.

Oliver Wendell Holmes, in 1855, was the first to notice that puerpural sepsis was contagious and likely caused by transmission from physicians conducting autopsies on cases of puerperal fever. Ignaz Semmelweis conducted a clinical trial on hand washing in the prevention of puerpural fever in the maternity ward of Vienna General Hospital. The results of this and another trial were published in 1861. These findings, along with those of Koch, Pasteur, and Lister ushered in an era of bacteriology and the study of infectious disease. In 1874, Gerhard Armauer Hansen, deduced from epidemiologic studies that M. leprae is the cause of leprosy. To overcome his critics, in 1880 he inoculated patients and nurses with the bacillus to show causality. This was done without consent. Walter Reed, in studying the mosquito as a vector for yellow fever, obtained informed consent from all his volunteers, and noted as much in all his publications.

1.12 Antibiotic Era (Fig. 1.2)

In 1925, Abraham Flexner issued a report requiring a rigorous scientific basis for medical education. In 1928, Scottish physician Sir Alexander Fleming, discovered penicillin, and essentially gave birth to a pharmaceutical industry, beginning with antibiotics. In the 1930s, the first generation of antibiotics was discovered. This included the beta lactams, sulfa drugs, the aminoglycosides, and chloramphenicol. In the 1950s tetracyclines, macrolides, and quinolones were developed [11]. For the next two decades, antibiotic research languished and any subsequent antibiotic advances were in the form of incremental, so-called "me too" drugs. Some analysts have blamed this drought on the FDA's statistical requirements for proving noninferiority. The FDA relaxed their requirements in a meeting with PhRMA and IDSA (Infectious Diseases Society of America), however relations between the FDA and industry reached another low point in 2006 in the wake of the telithromycin (Ketek) trial, which resulted in withdrawal of approval of a drug that caused rare but serious liver toxicity. Most companies have withdrawn because:

- Clinical trials for antibiotics are becoming more expensive because more targets of efficacy (species of organism, and site in the body) are required to show noninferiority over competitors.

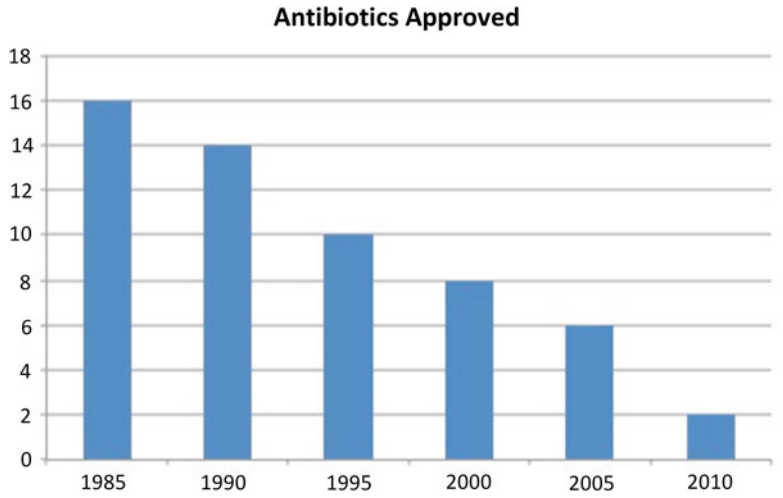


Fig. 1.2 The number of new antibiotics approved by the FDA has declined precipitously. *Source*: H. Boucher Pew Charitable Trust Meeting

- Companies are more interested in chronic diseases. Antibiotics are for short-term use only. The net present value (NPV) of a drug represents its lifetime earnings minus its lifetime costs. The NPV of antibiotics has been $1.1 B compared to $11 B for SSRIs (selective serotonin reuptake inhibitors) and $15 B for statins.
- Resistance makes products less effective and less profitable. Stronger agents are held in reserve in small stockpiles in a few hospitals, also reducing profitability for companies.

The need for antibiotics could not be greater, with resistance increasing, and with the emergence of the so-called ESKAPE pathogens (*Enterococcus*, *Staph*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Enterobacter*). This family of pathogens is responsible for a growing number of serious infections of the skin and other organs and has few effective treatments [12, 13]. If regulatory costs prohibit advances in treating these infections (for example, nanoparticle trapped nitric oxide), manufacturers may develop and market the next generation of antibiotics outside the US. To reduce costs and promote innovation, some companies are banding together. Bristol-Meyers Squibb and Gilead Sciences came together on making a combination HIV pill. Merck published the crystal structure of HIV protease for competitors to use.

1.13 Industry and Regulation

During World War II and after, pharmaceutical research became a large enterprise sponsored by government and industry. Large numbers of trials were conducted on captive volunteers, such as military personnel, prisoners, and institutionalized

individuals (mentally ill, orphans, physically handicapped). In fact, many large academic medical centers and pharmaceutical companies had their research sites located near institutions, sometimes just across the street. Mishaps, tragedies, and cases of wartime and peacetime abuse led to ethics convocations and the promulgation of laws protecting human subjects and empowering agencies such as the FDA to develop guidelines to ensure the safety and ethical conduct of clinical research involving human subjects.

The US began receiving counterfeit and ineffective drugs from Mexico, leading to the Import Drugs Act of 1848. In 1905 Upton Sinclair's "The Jungle" exposed unsanitary conditions in the Chicago meatpacking industry. This instigated legislation requires processing inspections, and forbidding interstate and foreign commerce in impure and mislabeled foods and drugs.

The Food and Drug Act of 1906 did not require drugs to be effective, just that they meet standards of strength and purity. Before the act, drugs were commodities, and their contents were secret, hence the name patent medicine. In 1938, after 107 deaths due to "Elixir Sulfanilamide" the FDA required manufacturers to prove drug safety before marketing.

In 1947, the Nuremberg Code required informed consent prior to participating in experiments. In 1962, the Estes Kefauver-Harris Amendment led to requirements of teratogenicity and reproductive effects of drugs to be added, following the thalidomide phocomelia epidemic. During the Bay of Pigs in 1961, 1,200 men were captured, and ransomed from Cuba for $50M of drugs and supplies donated by the US Pharma. In return, they got tax deductions, and political good will. This resulted in the Drug Abuse Control Amendment of 1965, making it a crime to infringe on drug copyright or branding, leading to penalties, seizures of assets, or imprisonment.

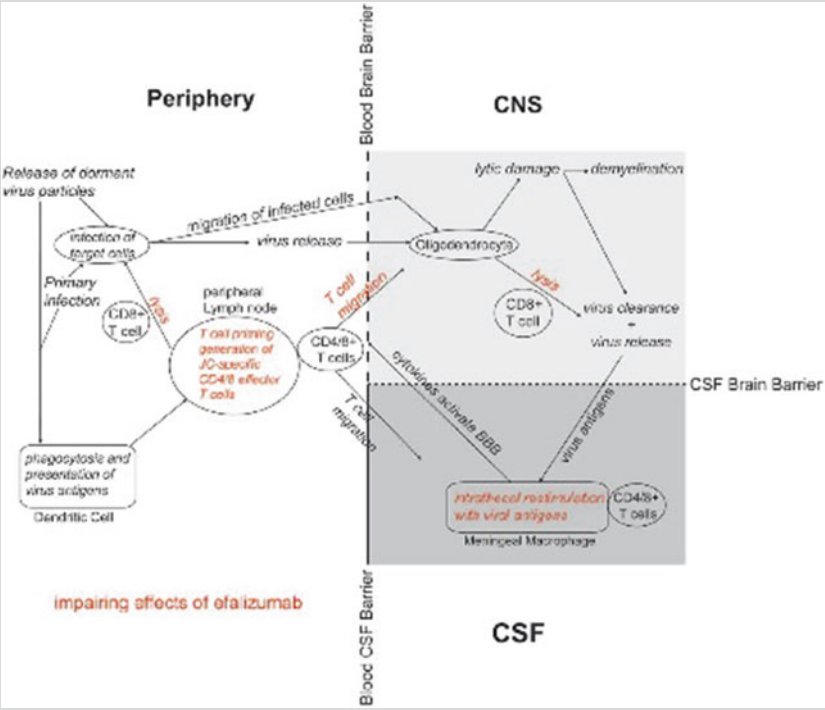
In 1982 the maker of Tylenol recalled 31 million bottles, valued at $100 M, and developed tamper-proof bottles. The Anti-Tampering Act passed in 1983, requires tamper-resistant packaging, and makes tampering a crime. The focus of the FDA has evolved over the last few decades: 1970s– 80s randomization and blinding; 1990s metabolism; 2000s safety (suicides on antidepressants, statin myopathy, aprotinin and surgical blood loss, Cox-2 and heart attacks, efalizumab and progressive multifocal leucoencephalopathy, topical immunomodulators and skin cancer risk, tacrolimus and Netherton syndrome) led to the FDA's 2007 Amendments Act, with an emphasis on risk mitigation and pharmacovigilance. Now the emphasis seems to be on comparative effectiveness research.

1.14 Protocol Design

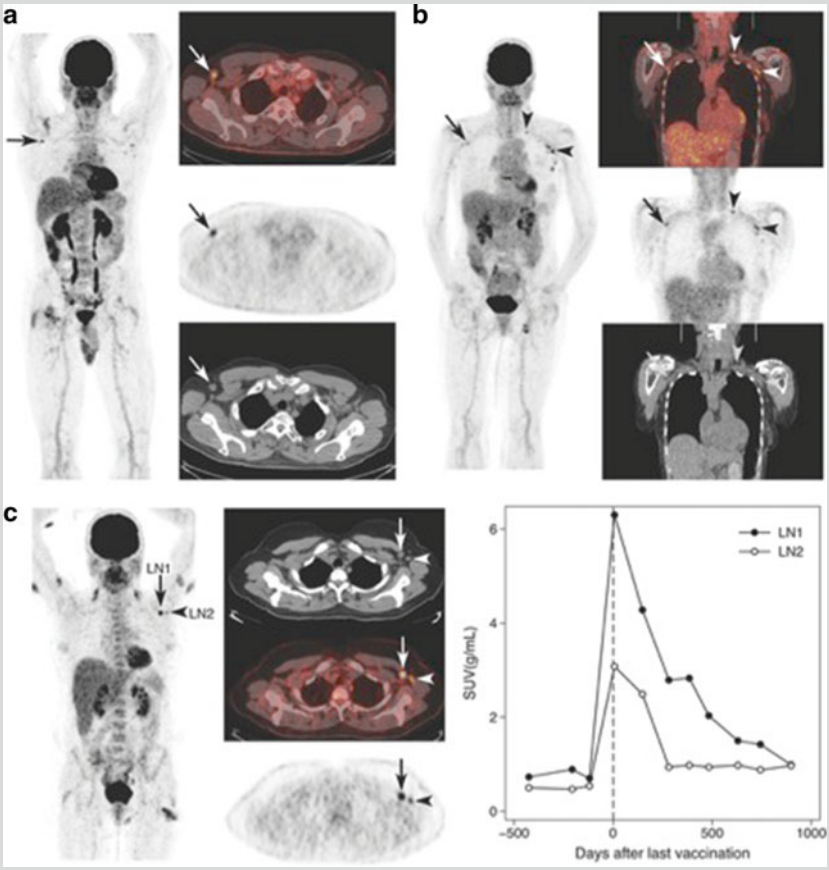
Sponsors typically provide sites with an identical protocol which cannot be modified. Some sponsors will reserve funds for small investigator-initiated studies, especially if they want to create good will at the site. Usually, these are conducted at large academic medical centers, with funding through grants, which are written by the investigators.

Inset 1.1

Nanotechnology clinical trials in melanoma. Matter behaves differently on the nanoscale. Its behavior depends upon its size, surface potential, surface reactivity, surface-to-volume ratio, shape, and other properties. One recent way to augment cell-mediated immunity has been to couple antigens to nanoparticles and immunostimulatory compounds. A small Phase-I trial in Europe examined the effect of a nanoparticulate vaccine combined with Toll-like receptor agonists on memory cells in melanoma subjects.



Goldinger SM, Dummer R, Baumgaertner P, Mihic-Probst D, Schwarz K, Hammann-Haenni A, Willers J, Geldhof C, Prior JO, Kündig TM, Michielin O, Bachmann MF, Speiser DE. Nanoparticle vaccination combined with TLR-7 and -9 ligands triggers memory and effector CD8⁺ T-cell responses in melanoma patients. Eur J Immunol. 2012 Nov;42(11):3049–61.


a
b
c
LN1
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SUV(g/mL)
Days after last vaccination
LN1
LN2
6
4
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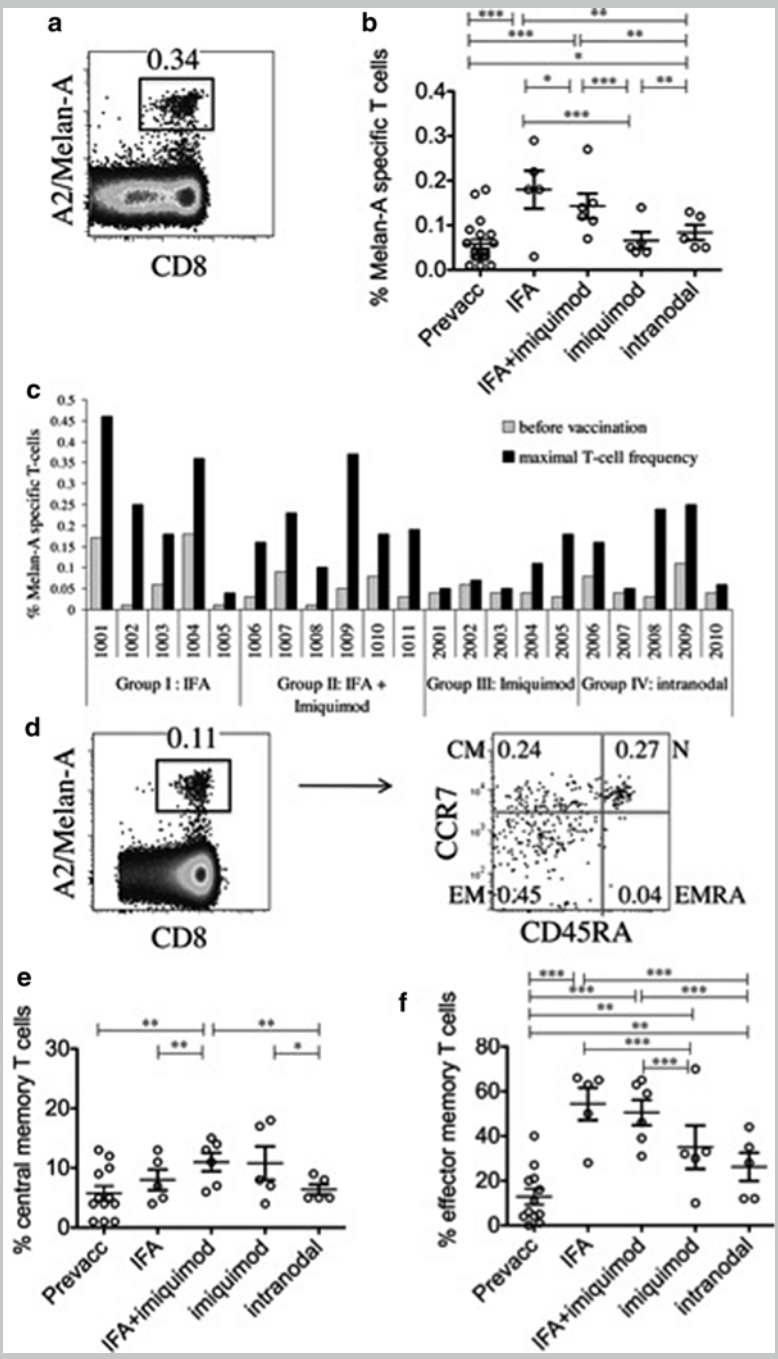
a
0.34
A2/Melan-A
CD8
b
% Melan-A specific T cells
Prevacc
IFA
IFA+imiquimod
imiquimod
intranodal
c
% Melan-A specific T-cells
before vaccination
maximal T-cell frequency
1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Group I : IFA
Group II: IFA + Imiquimod
Group III: Imiquimod
Group IV: intranodal
d
0.11
A2/Melan-A
CD8
CM 0.24 0.27 N
CCR7
EM 0.45 0.04 EMRA
CD45RA
e
% central memory T cells
f
% effector memory T cells

When you undertake a clinical investigation, your guide is a protocol. Whether you write your own protocol for an investigational new drug or device, or obtain a protocol from a sponsor, it contains stereotypical elements. Typical protocol components include:

- *Introduction*: This section explains the illness, and the rationale for the intended drug or device.
- *Objectives*: These depend on the phase of the study, early phase objective might be tolerability, while later phase objectives might be safety and efficacy.
- *Plan*: This section discusses the details of the study. The size of the study, the targeted treatment populations, and the arms or study treatment groups are described here.
- Inclusion/exclusion criteria spell out in as much detail as possible who may or may not participate in the study.
- *Methodology*: This is a step-by-step guide to each study visit. Elements include instructions for examining subjects, photographing skin lesions, taking biopsies, administering medication, and entering data in an electronic case report form. This section should be written clearly enough and in sufficient detail that any outside person could reproduce the study.
- *Termination criteria*: This covers end points, such as improvement in Psorasis Area and Severity Index (PASI) score by 10 %. This section often requires a statistician's help.
- *Adverse events*: This section has a clear definition of adverse events and severe adverse events as well as clear reporting guidelines and reporting timelines.
- *Laboratory procedures*: Covers special tests that the study may require, such as venipuncture, or electrocardiogram, biopsy, or imaging.
- *Administrative*: This section details the administrative responsibilities of the site, the sponsor, any contracting group such as a CRO or SMO, and any regulatory agency such as an IRB or the FDA.
- *Statistical plan*: This shows the rationale for the size of the study and the breakdown of the subjects. One ethical principle for studies involving human subjects requires using as few subjects as necessary to answer a clinical question. Statisticians are a crucial member of the research team and are the best allies to determine study size and design.
- *Study personnel*: Lists the minimum personnel required to conduct the trial safely. Reading the protocol helps you decide your staff requirements and helps you determine a budget. You may be able to delegate some of your staff to multiple studies, but other staff (such as clinical research coordinator) you may want to dedicate exclusively to one study.
- Appendices.
- *Informed consent*: This is not just a document, but a process. The informed consent should be clear, easy to understand, and an integral part of all your subject evaluations.

Patient Mix

- *Inclusion criteria*: This section will have a careful definition of illness and a detailed description of the volunteers who are eligible to participate in the study. It will include items like age, gender, pregnancy status, health status, approved medical history, approved concomitant medications, disease type and severity, as well as any hurdles subjects may face that may affect their eligibility status (such as transportation to and from the clinic).
- *Exclusion criteria*: This section will contain any criteria which may preclude subject participation in the study. These criteria include: allergy, health factors which may make a subject at increased risk for adverse reactions. This section can protect protocol integrity by excluding those too ill to demonstrate a benefit, those with underlying diseases that affect the evaluation of a drug's efficacy or safety, and those who have received medication without an adequate washout period. Unwillingness to give informed consent is a universal exclusion criterion.

Protocol type: Studies can be observational or interventional; cross-sectional, prospective, or retrospective. Interventional studies can be randomized or not.

- *Parallel study*: Each participant is assigned to a specific arm, but all other activities are the same for all participants. This was first done in 1747 by James Lind to establish the treatment of scurvy, and was also criticized because of lack of consent.
- *Crossover study*: Patients begin with one drug and then switch, thus serving as their own internal references or controls. Effects are then attributed to the drug rather than intersubject variability. In "double dummy" protocols, the drugs are disguised so that the patient can't tell the difference between drug A and B.
- *Blinding*: In open label trials, there is no blinding; in this case, all participants know which treatment the subjects are getting. This is more common in cancer trials or orphan drugs. In single blinding, the subject does not know, and in double blinding, the investigator and subject do not know who gets drug. Double blinding is typically done in phase III.

1.15 Device Development

Medical device trials: Medical devices contribute enormous billions to the worldwide economy. They add to a US trade surplus and attract huge venture capital investments. Devices are classified according to their use and risk.

Definition: Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article…that is recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body…and which does not achieve any of its primary

intended purposes through chemical action…and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

- *Class 1*: Devices in this category pose minimal risk, and are exempt from regulation. Most made before 1976 (elastic bandages, exam gloves, dermatoscopes), about 47 % of devices fall into this category. If a new device is substantially equivalent to one that is already marketed, it can be exempt from a premarket notification application.
- *Class 2*: Includes about 43 % of devices. Devices in this category typically pose moderate risk, if substantially equivalent to one already in existence, the FDA requires a premarket letter of notification or 501(k). Examples: EKG machines, contact lenses, IV catheters, Foley catheters, endoscopes, laparoscopes, and lasers.
- *Class 3*: Poses a significant risk and tend to be implanted. They always require a premarket approval application. Examples include prosthetic valves, artificial joints, invasive monitoring devices, angioplasty catheters, and ventilators. Sponsors decide what is significant risk (not the FDA), but this decision can be challenged by the FDA or the IRB. There is a humanitarian device exemption (HDE) for a device used in <4,000 patients/year. The 21 CFR part 812 outlines regulatory requirements in the Investigational Device Exemption (IDE). Device trials can depend on the technical skills of the investigator (i.e., hip replacement). Adverse events are reported through UADE (unanticipated adverse device effect). These can lead to recalls, which is a problem for implants, such as Sprint Fidelis defibrillator leads, which failed and fractured, leading to shocks and deaths.

Patients have no legal protection for faulty devices. A manufacturer cannot be sued if a device receives marketing approval from the FDA. One test case which solidified this industry protection was the US Supreme Court ruling Riegel vs. Medtronic. The Medical Device Safety Act of 2009, an attempt to address patient protection, is still in committee. The Medical Device User Fee Amendments of 2012 (MDUFA III) takes effect since October 1, 2012. When medical device companies register with the FDA, they will pay user fees, which will allow the FDA to have the resources to review device surveillance, and speed the decision making and appeals processes.

Critical Path Initiative has a Medical Device Innovation Initiative passed in May 2009 to expedite CDRH approved device development. Device trials are shorter than drug trials, around 18 months. The life cycle of devices is less than 2 years because of new technology and obsolescence.

Regulation is faster in Europe than in the US because trials are nonrandomized feasibility studies of less than 100 patients and safety-only demonstrations.

Combination products (prefilled syringes, MDI, transdermal patches). These are a combination of a drug prepackaged in an administration device or delivery device. They are more difficult to make, and have more regulation to deal with, but can be safer. Examples include sirolimus-eluting coronary stents by J&J (CYPHER). Dermatology drug/device combinations include premixed syringes for the delivery of biologic therapies for psoriasis, and canister/drug combinations for the delivery of foam-based topical formulations. Whether a combination product is reviewed by CDRH or reviewed by CDER makes a big difference. The assignment is determined

by the primary mode of action. Drug eluting stents are regulated as devices, but drug eluting disks for targeted chemotherapy are regulated as drugs.

Problems with device trials: Indemnification is a big issue because many are surgically implanted. They require uncompensated training of investigators. Institutions may get less reimbursement for appearing state-of-the-art. Postmarket surveillance may be required for 5 years, which is expensive. It's hard to get Medicare to pay for devices. Now devices cost $76B annually, profits are over 20 %. Device trials may have conflict of interest because investigators or inventors may have equity interest in the device and the technical capability of using/implanting them. Furthermore, some devices are very expensive (for example, dermatology lasers for cosmetic use). There is a significant financial conflict of interest for investigators if manufacturers donate or offer a device at a steep discount in exchange for conducting research, especially if the research requires minimal effort on the part of the investigator, or is of dubious merit or quality.

1.16 Phases of Drug Development

There are many reasons for conducting clinical trials. These include economic support, fulfilling institution requirements for tenure, gaining acceptance in your research group or academic department, gaining recognition from your peers, getting published, and giving back to patients and society [14].

Medication research involves a "Life Cycle" which starts with observation of a clinical or basic science phenomenon (Fig. 1.3). The observation leads to testable hypotheses, which point the way to a biological mechanism of disease. Confirmed hypotheses lead to potential diagnostic tools or therapies which are further tested and refined in preclinical and clinical phases. In the post-marketing phase, feedback from the "real world" of the clinic generates new observations, which lead to further testable hypotheses, and the cycle continues. Thus clinical research begins and ends with humans in our environment.

The FDA has several focus centers: CDER (Center for Drug Evaluation and Research), is responsible for the safety of chemically synthesized drugs. CBER (Center for Biologics Evaluation and Research) is for vaccines, blood and tissue products, and cellular or gene therapies. Biologics are biotech-based mixtures derived from living sources. CDRH (Center for Devices and Radiological Health) looks at IV catheters, pacemakers, implantable pumps, synthetic grafts, and breast implants. Devices have slightly different regulatory requirements, although these are changing, depending on their potential to do harm.

In 1992 the Prescription Drug User Fee Act (PDUFA) was passed [15, 16]. The fees were used to hire more reviewers at the FDA to speed the approval process. It was reauthorized in 2007. IOM criticizes the PDUFA for conflict of interest. The IOM believes the excess fees are used to support expedited approval at the expense of safety. In Europe, approval is faster, and the withdrawal due to safety is about the same as in the US, 3 %. Some withdrawn medications were prescribed millions of times (Seldane, Hismanal, Propulsid, Rezulin, Bromfenac, Fenfluramine).

Fig. 1.3 Kelsey and Kennedy

None of the withdrawn drugs were for life-threatening conditions. In no case was the prescribed drug the only alternative available. Recalls of Ketek, Vioxx and Baycol led to congressional investigations. Currently, based on these recalls, the Institute of Medicine recommends: stricter labeling requirements and advertising limits; additional enforcement tools for the FDA; mandatory registration of clinical trials; increased role of the FDA drug safety staff; a significant boost of FDA funding [17–20]. One of the principle examples of high-profile drugs withdrawn from the dermatology market is efalizumab [21–23]. Efalizumab (Raptiva) is a monoclonal antibody against LFA-1 (leucocyte functional antigen-1). This is an adhesion molecule present in T-lymphocytes which binds ICAM-1 (intercellular adhesion molecule-1). When T-cells bind ICAM-1 at endothelial sites of inflammation, they exit the circulation and invade the skin. Efalizumab interferes with this process and prevents T-cell egress from blood vessels. In clinical trials demonstrated safety and efficacy, efalizumab was approved for the management of psoriatic arthritis and psoriasis. Subsequent post-marketing surveillance led to its withdrawal because of several reported deaths of patients from progressive multifocal leucoencephalopathy.

1.16.1 The Modern Era

- Rules and regulations are evolving to keep pace with developments in technology, such as recombinant DNA technology, and nanotechnology. Nanotechnology has experienced an explosion in development over the past two decades in consumer products and in medicine. The greatest number of new patents incorporating nanotechnology over the past decade have targeted the skin in products ranging from sunscreens, to topical delivery and systemic medications, to diagnostic devices. One of the earliest nanoparticulate drugs to be approved was liposomal doxorubicin, which is used for the treatment of

Kaposi sarcoma [24]. Nanotechnology is the study of particles 100 nm or smaller in size. The vast majority of biologically important processes (nucleic acid replication, enzyme activity, cell membrane interactions, etc.) occur in the nanometer size range. Matter is known to behave differently at the nanoscale. Drug and device developers are capitalizing on these new properties of matter to create novel tools for the maintenance of skin health, and the diagnosis, and management of skin disease. There have been concerns expressed about the potential toxicity of nanomaterials, and a call for the FDA to offer guidelines for the public and industry in this arena [25]. In 2013, the FDA, issued a special policy on nanomaterials for public comment:

FDA will continue to regulate nanotechnology products under its existing statutory authorities, in accordance with the specific legal standards applicable to each type of product under its jurisdiction. FDA intends to ensure transparent and predictable regulatory pathways grounded in the best available science.

- One size does not fit all. We intend our regulatory approach to be adaptive and flexible. It is necessary for technical assessments to be product-specific, taking into account the effects of nanomaterials in the particular biological and mechanical context of each product and its intended use.
- Particular approaches for each product area will vary according to the statutory authorities. The scope and issues covered in the two draft guidance documents released today—one for foods and one for cosmetics—reflect this approach.
- FDA's regulatory policy approach is consistent with relevant overarching U.S. government policy principles, and supports innovation under appropriate oversight.

Industry remains responsible for ensuring that its products meet all applicable legal requirements, including standards for safety—regardless of the emerging nature of a technology involved in the manufacturing a product. *FDA encourages industry to consult early with the agency to address any questions related to the safety, effectiveness, or other attributes of products that contain nanomaterials, or about the regulatory status of such products.*

Inset 1.2

Example of a prospective study showing the role of the environment in psoriasis:

Sixty obese volunteers were enrolled in a prospective trial and placed in either a control or intervention group. Subjects with a body mass index 27–40 were included, and were between 25 and 71 years of age. A low-calorie diet (called Low-Energy Diet or LED in the study) group was given an 800–1,000 kcal/d diet for 8 weeks and allowed to return to 1,200 kcal/d in the following 8 weeks. The control group was simply told to eat a healthy diet. The LED group lost an average of 15.4 kg and had modest improvements in PASI (a drop of two points) and DLQI (a drop of two points).

Jensen P, Zachariae C, Christensen R, Geiker NR, Schaadt BK, Stender S, Hansen PR, Astrup A, Skov L. Effect of weight loss on the severity of psoriasis: a randomized clinical study. JAMA Dermatol. 2013 Jul;149(7):795–801.

The FDA is examining novel nanotechnology-based applications on a case-by-case basis and urging close consultation and guidance at the early stages of development in order to maximize patient safety and minimize unnecessary or inappropriate or inadequate studies.

Issues such as ownership of tissue and genetic material are being debated in the courts [26]. The famous case of Henrietta Lacks and cell culture lines derived from her tissues without consent have been well-documented abuses. More recently, participants in clinical trials have contested patents derived from their tissues and genetic materials. Courts have generally sided with companies and patent holders, denying research study volunteers ownership rights or royalties from any intellectual property derived from their participation. In 2013, the US Supreme Court, in an apparent reversal of judicial precedent, raised the bar on patenting of genes and genetic material, making its patenting more difficult for manufacturers.

Data Mining: Direct Patient Identifiers (DPI) missing from data suitable for mining should include:

- Patient Name
- Patient Account Number
- Geography smaller than a state (Researchers may use the first three letters of a zip code for a population>20,000).
- Phone Number
- Fax Number
- Address (home, email, work, IP address)
- Insurance ID number
- Biometric data (iris scan, fingerprint, photo of face or identifying markers such as tattoos)
- License number (Driver's license, automobile plate)
- Any date except the year.
- Unique ID codes

Research is also in an era of big data. Projects such as the Cancer Genome Project are gathering enormous quantities of data on subjects, including personal information, demographic information, detailed case histories with thousands or millions of data points, and laboratory data including longitudinal and prospective gene sequencing data [27]. Subjects are located in the United States and the rest of the world. These massive archives of data are being made analyzed with powerful computers such as IBM's Watson to look for patterns that may not be obvious to human researchers. They are also being filtered through online medical decision support tools. The depth detail of the data, combined with online accessibility, albeit through secure channels, make the risk of data breach a real concern. The privacy of human subjects is harder to protect in the electronic era, and additional rules have been developed to ensure privacy and anonymity. Privacy is pitted against public interest in community studies and large population studies which try to electronically extract useful clinical and genetic data from hundreds, thousands, and millions of individuals. Data mining of this type requires unique identifiers to be missing (see Insets).

Regulatory agencies have experienced pushback from health care advocates and activists to speed up trials for life-threatening diseases such as AIDS and cancer. In some cases, social media have lit firestorms of activism including death threats against

Inset 1.3
Post-marketing surveillance led to the discovery of a disease association and efalizumab. The causal relationship between efalizumab and deaths from progressive multifocal leucoencephalopathy related to JC virus activation was not initially appreciated during the preclinical and Phase I–III stages of development. Once the association was made, additional pathways were generated regarding potential mechanisms and future testable hypothesis.

Schwab N, Ulzheimer JC, Fox RJ, Schneider-Hohendorf T, Kieseier BC, MonoranuCM, Staugaitis SM, Welch W, Jilek S, Du Pasquier RA, Brück W, Toyka KV, RansohoffRM, Wiendl H. Fatal PML associated with efalizumab therapy: insights into integrin αLβ2 in JC virus control. Neurology. 2012 Feb 14;78(7):458–67.

Inset 1.4
Disease Association of Melanoma and Parkinson's Disease. Data can be extracted from large databases using keywords or diagnosis codes. These can be used for retrospective or prospective analysis. The validity of the results is only as reliable as the quality of the database.

This was a 31 center trial with 2,106 patients, mean age 68.6, who were examined by a neurologist to confirm the diagnosis of Parkinson's Disease and a dermatologist for a total body skin examination. Any suspicious pigmented lesions were biopsied. Age and sex-matched melanoma risk was 2.24-fold higher than that in the SEER database.

Bertoni JM, Arlette JP, Fernandez HH, Fitzer-Attas C, Frei K, Hassan MN, Isaacson SH, Lew MF, Molho E, Ondo WG, Phillips TJ, Singer C, Sutton JP, Wolf JE Jr.; North American Parkinson's and Melanoma Survey Investigators. Increased melanoma risk in Parkinson disease: a prospective clinicopathological study. Arch Neurol. 2010 Mar;67(3):347–52

companies to target drug release for compassionate use on single individuals (http://www.newsobserver.com/2014/03/12/3696963/chimerix-ceo-faced-death-threats.html). Regulatory agencies have responded with fast-track protocols and compassionate use waivers. Complaints about the cost of drugs and devices have led to a push for comparative effectiveness research, which pits a new treatment against an established one.

The drive to increase the pace of approval, reduce the cost, and broaden the market of drugs and devices has led to the migration of clinical trials overseas. Regulatory agencies and sponsors are continually revamping their procedures, policies, and protocols to adapt to the ever-changing and competitive landscape of clinical research. Nowhere is this more true than in dermatology, where drugs, devices, cosmetics, and cosmeceuticals are being developed at an exponential pace to satisfy the needs and wants of a global audience.

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Chapter 2
General Clinical Trials

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2.1 Design of Trials

There are different types of clinical studies (Fig. 2.1). They can be divided into observational and clinical trials (interventional). Observational studies include cohort studies, in which a group of subjects are followed to analyze potential risk factors for developing a disease; case control studies, in which one group of people who have the disease of interest and another group who do not have the disease are compared to identify potential risk factors; and cross-sectional studies, in which an entire population is observed at one point in time to determine data such as disease prevalence or risks [1]. Observational studies offer helpful information regarding associations that may exist between certain exposures and outcomes. This information would be useful if a researcher is trying to determine if a group of people with a common exposure have a change in the risk of developing a certain disease [2]. For example, a case–control retrospective study by Robinson et al. sought to investigate whether the use of photosensitizing medications increased the likelihood of developing non-melanoma skin cancer. This observational study examined people who had a form of non-melanoma skin cancer (case) as well as those who did not (control), and determined how many from each group had been exposed to photosensitizing medications. The data showed that the use of photosensitizing medications may increase the risk of developing a form of non-melanoma skin cancer [3]. Because this study examined exposures from the past, it is considered a retrospective study. Studies that examine a present exposure and measure future outcomes are called prospective studies and they, too, offer useful information regarding links between exposures and outcomes [2]. Chen et al. conducted a prospective cohort observational study by identifying patients who had a

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A. Nasir (ed.), *Clinical Dermatology Trials 101: A Primer for Dermatologists*,
DOI 10.1007/978-3-319-09027-6_2

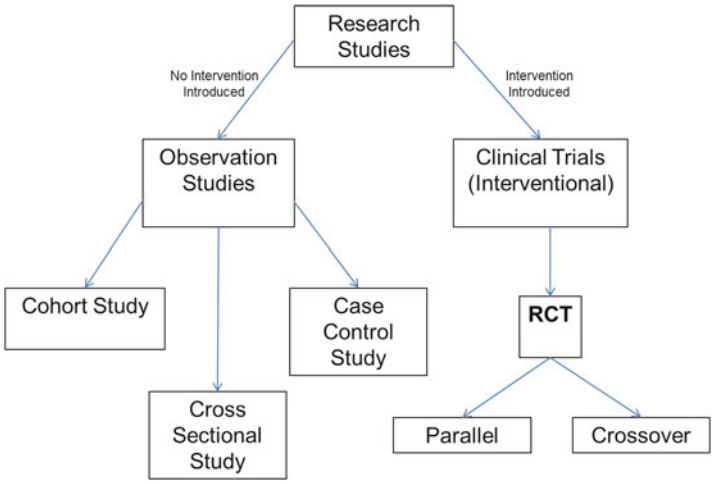


Fig. 2.1 A simplified overview of research study designs. Observational studies, where no intervention is introduced, include cohort, cross-sectional, and case control studies. In contrast, interventional trials include an intervention of interest and are most commonly designed as randomized control trials (RCTs) which can utilize parallel or crossover treatment and placebo groups

non-melanoma skin cancer that was treated either by electrodessication/curettage, general excision, or Mohs excision. These patients were followed to identify any recurrences of their skin cancer in an effort to determine if any of the treatment methods was superior in terms of reduced recurrence rates. The data collected showed that the difference in recurrence rates among the treatment methods was not statistically significant, which demonstrates that observational studies can help answer relevant research hypotheses [4]. However, while observational studies yield useful data, they utilize natural conditions and are not designed for clinical trials where medical treatment is introduced. Naturally, experiments are used to design clinical trials in which some form of intervention is studied [2]. The gold standard of an interventional clinical trial is the randomized controlled trial (RCT) [5]. RCTs are often considered the "gold standard" because it is the only proven method that can reduce bias by ensuring that those receiving the study treatment and those receiving placebo are as equal as possible in regard to known and unknown variables [6]. To bolster this claim, Schulz et al. credit randomization, avoidance of exclusions after entering the trial, and blinding as the keys to the RCTs superiority. They go on to state that studies that do not include these three criteria tend to generate questionable data [7]. Sackett et al. further support the idea that RCTs are the gold standard of clinical trials because they frequently provide useful outcomes and are so rarely misleading [8]. However, certain biases have recently questioned the validity of RCTs. As an example, a study of five empirical methodological studies has shown that RCTs that produce positive results, meaning that the item or drug under study in the RCT did produce a statistically significant result, are more likely to be published and published quickly than RCTs that create negative results, meaning the item or drug under study did not produce a statistically significant result. This effect is known as publication bias, and it argues that

because RCTs that produce positive results are more likely to be published, the RCT is itself a biased method of reporting data [9, 10]. Regardless of these arguments, however, RCTs are still widely used for designing clinical trials.

Inset 2.1

Example of a randomized trial:

Clobetasol propionate, 0.05 %, vs hydrocortisone, 1 %, for alopecia areata in children: a randomized clinical trial. Lenane P, Macarthur C, Parkin PC, Krafchik B, DeGroot J, Khambalia A, Pope E. JAMA Dermatol. 2014 Jan;150(1):47–50.

In this single-center trial, a low- and high-dose topical steroid were compared over a 24-week period on children ages 2–6 with alopecia areata of the scalp. The trial was blinded in a 2-arm parallel group. Topical steroids were applied for 6 weeks on and 6 weeks off for two cycles during the 24-week study period. The primary endpoint assessed was hair loss at the end of the study. Investigators noted a greater decrease in hair loss in the high potency group compared to the cortisone group. One subject in the high potency group had atrophy which resolved in 6 weeks. No systemic cortisol disturbances were observed.

In RCTs, two groups of patients are established: those receiving the treatment being studied, and those who do not receive the study treatment, but rather a placebo (or a previously established treatment) [2]. The advantages of this design allow for bias reduction through randomization [5]. Bias occurs when different variables such as age or gender are not balanced between patient groups and therefore sway trial results. Randomization refers to a patient being randomly assigned to either the treatment group or placebo (control) group once they have been screened and identified as being eligible for study participation [11]. Randomization reduces bias by randomly distributing these variables, ideally equally, between the groups [6].

Inset 2.2

Blinding or Masking

In a study of hypnotism, or mesmerism, Benjamin Franklin, and Antoine Lavoisier blindfolded (or masked) subjects to prevent them from seeing treatments before evaluating the claimed results. Though used interchangeably with blinding, masking implies eye openings and the ability to see what is going on. Because of potential confusion, blinding has become the standard term in the international clinical research lexicon.

Franklin B, Bailly JS, Lavoisier A. Rapport des commissaires chargés par le roi, de l'examen du magnetisme animal. Chez Gabriel Floteron: A Nice; 1785.

RCTs can be further modified by their design and degree of blinding. RCTs typically utilize a parallel-group design in which the two groups remain separate in their treatment setup, but everyone within each group is treated identically. Crossover studies are studies in which each patient receives both the study intervention and the control for equal but separate time periods. These also offer the benefit of further bias reduction since each patient serves as his own control [12]. Also critical to the design of a RCT is the blinding status. In a single blind RCT, the investigator is aware of a patient's treatment status, but the patient is not [11]. This design leaves the data vulnerable to experimenter's bias in which the investigator's knowledge of treatment status could influence his evaluation [13]. Double-blind studies eliminate this bias, as well as the placebo effect, because neither the investigator nor the patient is aware of treatment status [11]. An outside participant, typically an unblinded pharmacist, is the one who is aware of the patient's treatment status. An understanding of how RCT design and blinding allows investigators to develop the RCT that will investigate their hypothesis while limiting the degree of bias involved.

Inset 2.3
Example of a multicenter DBPCR randomized.

Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria.

Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. N Engl J Med. 2013 Mar 7;368(10):924–35.

This was a phase-three trial to evaluate the safety and efficacy of omalizumab in anti-histamine refractory chronic idiopathic urticaria. Volunteers were randomly assigned to receive drug at three different doses, or placebo, followed by a 4-month observation period. They were asked to score their itching. The baseline itching score was 14 in all four groups. It dropped to 9 in the placebo group, 8, 6, and 4 in the 75 mg, 150 mg, and 300 mg groups, respectively.

2.2 Phases of Drug Development

For a new drug to be approved by the FDA for commercial use, it must undergo a series of trials (Fig. 2.2). The process begins when a new drug is developed in a laboratory setting. Laboratory testing usually begins with cell studies, and ultimately graduates to live animal studies to determine *pharmacokinetics* and *toxicity* [14]. For this preclinical testing data to be considered acceptable to the FDA, it must comply with good laboratory practices (GLP). Adhering to GLP ensures that the data produced in the laboratory studies meet the minimum environment, personnel, and technique standards necessary to ensure reliable data. The specific goals that contribute to a successful preclinical trial include understanding basic

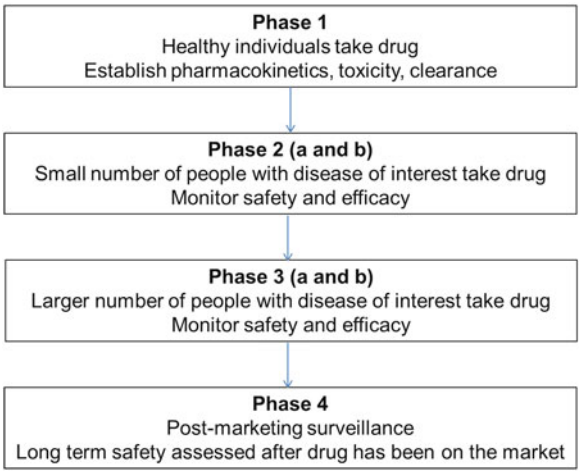


Fig. 2.2 A diagram of study progression. All investigational drugs or products that pass preclinical testing and are reviewed by the FDA are first tested in a phase 1 clinical trial and then progress to phase 2 and 3 trials. Once approved by the FDA, phase 4 studies continue to monitor the product for long-term safety purposes

pharmacokinetics of the drug, identifying drug toxicity levels in two different species of animals, and performing short-term toxicity studies that are approximately equal in time length to the actual drug treatment time [15].

Once acceptable standards are met in animal models, the drug is then studied in humans. This begins with a *Phase 1* trial in which a small number of healthy individuals take the drug. These participants are then studied to further establish pharmacokinetics and toxicity as well as drug clearance in humans. Again, once an acceptable standard is met, the drug passes to a *Phase 2* trial where its **safety** and **efficacy** are measured in a small number of patients who have the disease the drug intends to treat [14]. Of note, Phase 2 trials can be split into Phase 2a and Phase 2b trials. Phase 2a trials focus on proving the suspected mechanism of action of the drug and typically involve fewer patients than Phase 2b trials. Phase 2b trials strive to identify the ideal dosage of the study drug that allows for the desired efficacy while minimizing side effects [16]. If the drug is shown to be effective for the disease of interest, it is then tested in a *Phase 3* trial. Phase 3 trials continue to demonstrate efficacy and safety in patients who suffer from the disease of interest, but involve a much larger patient population and test the drug at different concentrations as well as in combination with other medications [14]. Similarly to Phase 2 trials, Phase 3 trials can be split into Phase 3a trials where the main goal is to generate sufficient data to demonstrate safety and efficacy, and Phase 3b trials which seek to support future publications [16]. Finally, when sufficient data has been collected, the sponsor of the drug submits a new drug application (NDA) to the FDA for final approval. *Phase 4* trials, or *post-marketing surveillance*, are conducted after an approved medication is on the market in order to test long-term safety of the medication [14].

Under the FDA Amendments Act (FDAAA) of 2007, pharmaceutical companies are tasked with maintaining standards of transparency regarding their study data. The main goal of the FDAAA was to ensure that the FDA received the necessary resources to review new trials; however, the act also impacted the degree of transparency of sponsor-initiated clinical trial data. The FDAAA requires "disclosure of any restrictions on public presentation or publication of results of studies funded by industry"

[17]. Now drug companies are required to make available to the public, information and results regarding their clinical studies, regardless of the stage of drug development. Most industries list their studies and relevant information regarding the studies and medications on their website so that the public can learn more about the methods, goals, and safety of current research. The public can also learn more about the multitude of clinical studies being performed by visiting www.clinicaltrials.gov.

2.3 Evolution of US Drug Law

Essential to the development of clinical trials are the drug laws that have established an acceptable degree of safety and efficacy for newly manufactured drugs. The first form of organized US drug law was developed in 1820 with the establishment of the US Pharmacopeia (USP), the first official list of standard drugs used in the United States [18]. Over time, the laws have evolved to keep up with advancement in science and engineering (Table 2.1). However, their goals remain the same—to ensure the efficacy of new investigational products as well as the safety of the patients who contribute to their development. Certainly their influence on clinical trials warrants a brief discussion of the history of their evolution and impact.

Before the direction and organization offered by drug laws existed, drug manufacturers didn't follow a standard protocol; this led to inconsistencies in drug development and sanitation. The consequences of these practices came to national attention in 1901. At that time, scientists were developing diphtheria vaccines by injecting *Corynebacterium diphtheriae* into horses and collecting their antibody-rich serum. However, due to a lack of sanitary protocol, thirteen children were killed after they were accidentally exposed to tetanus toxins incurred from this practice [19]. The tragedy led Congress to establish the Biologics Control Act, which was tasked with overseeing the safety and purity of vaccines. Five years later, the Biologics Control Act was molded into the Pure Food and Drugs Act of 1906 by then-president Theodore Roosevelt with the goal of blocking foreign trade of "mislabeled food and drug products" and prosecuting those who were found guilty of these practices [20].

Table 2.1 Brief timeline of US Drug Law Evolution

1820	US Pharmacopeia established
1902	Biologics Control Act
1906	Pure Food and Drugs Act
1911	US vs. Johnson
1912	Sherley Amendment
1927	Bureau of Chemistry Splits
1930	Regulatory Branch of Bureau of Chemistry is renamed FDA
1962	Kefauver-Harris Drug Amendments Act
1983	Orphan Drug Act
1998	Pediatric Rule
2003	Pediatric Research Equity Act

The law also required that each drug should have a label of active ingredients and should maintain a minimum drug purity level set by the US Pharmacopeia [21].

Whereas early US drug laws focused on purity and safety in manufacturing of drugs, more recent drug laws have focused on the importance of data from clinical trials in establishing the potential for adverse events and drug safety. In 1962, a new drug, thalidomide, gained popularity in Europe for its use as a sedative as well as an off-label use as a cure for morning sickness during pregnancy. However, doctors soon discovered that thalidomide was responsible for thousands of infants being born with phocomelia, or dysmorphic limbs [22]. Fortunately, the Food and Drug Administration (FDA) had not given approval for this drug due to FDA inspector Frances Kelsey's demand for data from clinical trials and for more convincing evidence that the drug did not cross the placenta [23]. The disastrous outcomes from this ordeal led to the development of the Kefauver-Harris Drug Amendments Act of 1962 which increased monitoring of drug approval processes as well as required clinical trial data demonstrating the safety and efficacy of new drugs before drugs could be approved.

After drug laws addressed the need for legitimate data from clinical trials for drug development, they shifted to focus on the different needs of specific patient populations. For example, in 1983, the Orphan Drug Act was passed which allowed the FDA to promote research for drug development for particularly rare diseases since they would otherwise not receive much attention [20]. Since this act passed, orphan drugs have continued to receive increased attention. As an example, the National Institutes of Health (NIH) has created the Therapeutics for Rare and Neglected Diseases (TRND) program that offers incentives for collaborators, including academic scientists, non-profit organizations, and pharmaceutical companies, to apply to work with NIH research teams to promote research efforts for new orphan drugs. The overall goal of these collaborations is to expedite the time necessary for a new drug discovery to progress through preclinical testing so that it may be a suitable project for pharmaceutical companies interested in developing the necessary clinical trials [24, 25]. In 1998, the FDA promoted the Pediatric Rule which extended the mandates of the Kefauver-Harris Drug Amendments Act to drugs that would be applicable to pediatric patients. This, in combination with the Pediatric Research Equity Act of 2003, which grants the FDA authority to mandate that sponsors conduct research for pediatric applications of investigational drugs, ensured that research for new drugs adequately addressed the needs of pediatric patients [20]. Obviously, medical knowledge continues to expand and offer new therapies to different patient populations. Just as important, however, is the fact that drug laws continue to evolve and direct drug development to protect the patients who need them.

2.4 How to Initiate Clinical Trials or Start a Clinical Research Site

There are three main characteristics that Sponsors and contract research organization (CRO's) look for in a site that is interested in doing clinical trials: the principal investigator (PI) qualifications, site adequacy, and patient population.

2.4.1 PI Qualifications

You don't have to be in an academic institution to become a PI. In fact, by 2005, 70 % of all the clinical trials in the United States were done in a private practice setting [26]. Several reasons for this shift are: the lower cost and administrative burdens in private practice settings and the gag clause (that prevent investigators from utilizing, analyzing, or publishing data from the trial without consent of the Sponsor) [26, 27]. Regardless, you should be able to prove that you are a good candidate. What steps should you follow?

(a) *Gather information and learn the basics of clinical research trials*: Read books (reading this book is a good start); utilize online resources; understand good clinical practices (GCP) and get formal training if needed. There are a wide range of training opportunities available from conference sessions to fellowship programs and even new master's degree programs in clinical research targeting MDs (see "Useful Links" in References section).
(b) *Do some networking*: Talk to the medical representatives about your interest in clinical trials; they will be able to direct you to the proper persons in their companies. Stop by the pharmaceutical booths in your medical organization meetings and meet the medical liaison team. Register online for the different Sponsors' investigator databases. Join or attend a clinical research organization such as the ACRP (Association of Clinical Research Professionals), SOCRA (Society of Clinical Research Associates) or the MAGI's (Model Agreements & Guidelines International) Clinical Research Conference.
(c) *Show your experience/expertise*: Your curriculum vitae (CV) or resume should reflect your experience as a clinical investigator. Start as a sub-investigator with a mentor. If you don't have any experience, do you have a particular area of expertise? Do you have publications that support your experience in that particular field?

2.4.2 Site Adequacy

You should have dedicated clinical trials space for equipment and supplies and sufficient staff qualified to perform the different tasks required by the study protocol.

(a) *Facility*: You need to show the Sponsor or CRO that your facility is suited to conduct a clinical trial. This includes enough space to conduct the visits and ensure the privacy of the subjects. Specific requirements are listed on Table 2.2. If you don't have laboratory facilities you may be able to use a nearby laboratory to draw blood and process samples. It is important to have a multidisciplinary network in case the protocol calls for specific assessments such as X-rays, ophthalmologic evaluation, etc.
(b) *Staff*: The success of a clinical site depends on having an engaged, enthusiastic, interested PI and a knowledgeable, experienced study coordinator. The PI should have committed time for research including (but not limited to) perform-

Table 2.2 Site requirement

(a) Adequate files, cabinets, storage space
(b) Refrigerator for storage of the investigational product
(c) Thermometer to monitor refrigerator temperature
(d) −20° freezer to store blood samples
(e) Access to dry ice
(f) Computer with internet
(g) Copier and fax machine

Inset 2.4

The Sponsor Team

- *Clinical Research Associate (CRA)*: The CRA is also called the monitor. Budget time to meet with the monitor and try to make a good impression. A typical trait for a monitor to have is compulsive attention to detail. The frequency and intensity of monitor visits vary with the experience of the investigative site, the complexity of the trial, and the dictates of the protocol. The monitor makes sure that your site is conducting a study according to the protocol, that your data are accurate, complete, contemporaneous, legible, attributable, original, and enduring. The monitor makes sure any deviations from the protocol are adequately explained. The monitor ensures that adverse events are promptly and correctly addressed. The monitor takes your questions and concerns back to the sponsor for feedback. Your monitor is a dedicated, knowledgeable professional, who may have even been a CRC once. Be very courteous, respectful, and attentive to your monitor's needs. A good relationship with your monitor will make your study go very smoothly. Your monitor may also be in the loop for a variety of studies, and will likely recommend you and your site if you perform well. Pay close attention to any concerns your monitor has. These should be addressed promptly, courteously, and professionally. Your monitor knows the protocol, and has been to a number of sites to see how the protocol is executed. Any lapses or concerns your monitor observes including out-of-date training certificates or unsigned documents or disorganized documents should be taken seriously. By doing so, not only will you improve the quality and timeliness of your work, you will avoid trouble in case of an audit. You will also save money, and make your monitor and sponsor happy. Visits can last from 4 h to several days. Disorganization costs money. Monitor visits to disorganized sites take longer, and often require revisits to ensure accuracy of data. This means more travel costs and more time costs for the sponsor. Your CRA may also be monitoring several sites (typically 5–10). If your site is not organized, you will be costing the monitor time away from family and from other sites.
- *Medical Research Associate (MRA)*: The MRA an in-house CRA at the sponsor's facility. The MRA may oversee CRAs and studies and monitor

subject safety, and make sure that all procedures are conducted in accordance with the protocol. The MRA may have been a CRA in the past and may be tapped to cover for your CRA if he or she is on leave or vacation or transitioning to another study. Give the same courteous treatment to your MRA that you do to your CRA.

- *Sponsor*: This is the overall developer of the drug or device. The sponsor oversees the development of a device from its initial chemical identification all the way through manufacturing, testing, approval, marketing, and post-marketing phases. The sponsor finances all aspects of a study from designing the trial, to providing materials, collecting data, monitoring trial, auditing all procedures and data to support the application to the FDA. Sponsors also keep investigators informed about the drug, including new safety information.
- *Medical monitor*: a physician at the facility who is on call for questions about the protocol or safety issues.

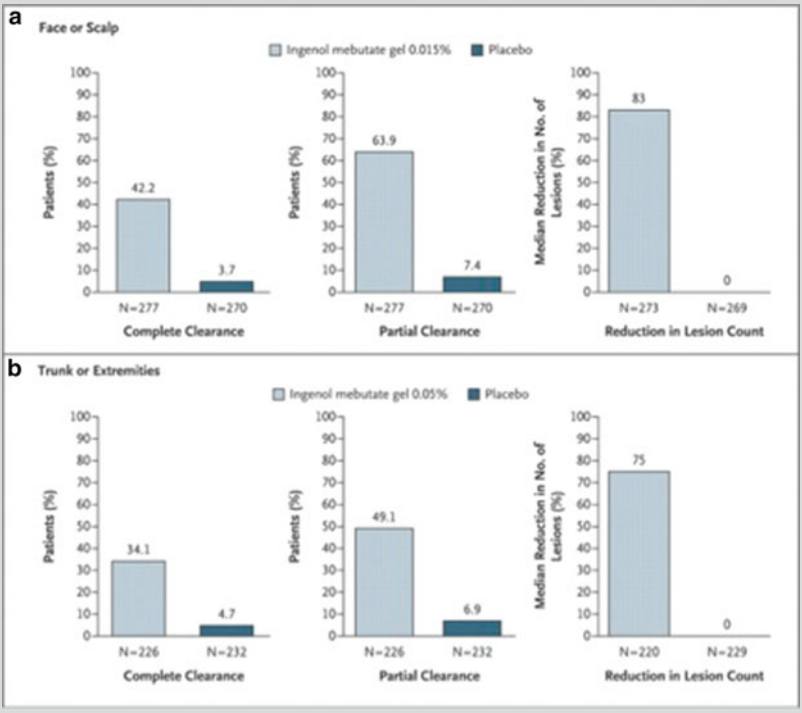
ing assessments during study visits, making time to meet with the monitors, travelling to investigator's meetings, reviewing safety lab results, and reviewing amendments to the protocol. The site should have adequate dedicated personnel to perform the protocol activities and respond to queries and requests by the Sponsors or CROs. If your study coordinator does not have experience, you could pay for them to receive formal training or certification.

(c) *Patient population*: Sites must have the adequate study population for the particular study. Sponsors are looking for sites that can recruit and enroll subjects fast. Their goal is to do the trial in a timely manner and at the same time have high quality data and minimal queries. You should be able to answer these questions: Do you have a database of your subjects for the particular disease being studied? What is your recruitment plan? How fast can you screen and enroll the subjects?

Inset 2.5

Large multicenter trials are often complex and involve several sites. They can be expensive to conduct. They are often more time consuming for investigators because there are more documents, and adverse events to review. The trial below has pooled data from a number of sites and has a detailed Supplementary Appendix to satisfy reproducibility requirements.

Four large multicenter randomized double-blinded studies examined the response to placebo or ingenol mebutate gel. The number of actinic keratosis on either the face and scalp or trunk and extremities were assessed during the study. Data were pooled from similar skin sites and compared.



Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012 Mar 15;366(11):1010–9.

2.5 Factors Influencing Site Selection

Even if you have the qualifications, adequate facilities, staff and patient population, you may not be selected for a particular trial (Table 2.3). Sponsors and CROs are keeping metrics on every site they work with and they try to minimize unknowns when possible. Sponsors prefer to work with sites they have worked with in the past who have a proven track record. Starting clinical trials at a new site takes patience, a good work ethic, and the ability to determine if a given protocol is worthwhile.

Table 2.3 Factors influencing site selection

(a) Lack of experience of PI
(b) Time constraints
(c) Cost of running the trial
(d) Legal liability
(e) Conflicts of interest with industry
(f) Cost-effectiveness (academic sites usually cost more than private sites)
(g) Enrollment below expectations
(h) Diversity and complexity of regulations
(i) Competing studies at the site
(j) Slow IRB committee approval
(k) Lack of experience/training of site personnel
(l) Lack of specialized equipment for the specific trial

2.6 Evaluating the Feasibility of a Protocol

The site start-up process involves not only a significant amount of administrative documentation but also a critical evaluation of whether the site has the ability to perform the study as outlined in the protocol, also known as a feasibility assessment. Sites are usually contacted by a representative of the sponsor or CRO and asked to fill out a feasibility questionnaire. The questionnaire may show up in an email as an attachment or as a link to an online questionnaire that should be completed as soon as possible. The responses are used to determine if a site meets the basic requirements of the clinical trial protocol. This may involve providing basic information about PI interest in the protocol, site staff, clinical research experience, available equipment, and several questions about the patient population at that site.

2.6.1 Patient Population

It will be expected that sites provide number percentages of a given subset of patients to estimate the likelihood that a given site will be able to enroll subjects that meet the inclusion and exclusion criteria. If at all possible these numbers should be based on an analysis of the patient database as opposed to guessing. The answers provided on the questionnaire will determine if the sponsor selects a given site to move forward in the site selection process. Be mindful that the HIPAA privacy rule applies to researchers who work for a covered entity (e.g. a hospital) and therefore it is important to understand how personal health information (PHI) can be used prior to a subjects' signing of an authorization to use PHI [28]. This rule affects institutional sites more frequently than community sites, however, protection of patient privacy is important for every site and processes should be established and documented.

2.6.2 Site Selection

The site selection process usually involves a site qualification visit to allow a sponsor representative or designee, a clinical research associate (CRA), time to meet with key site personnel, review the inclusion and exclusion criteria of the study, evaluate equipment, and tour the site facilities and drug storage areas. These visits not only allow the sponsor to verify the information provided in the questionnaire, but also allow the principal investigator (PI) to determine if they are truly interested in the protocol and have the staff and resources needed to be successful. The PI will likely be notified via email if their site has been selected and then be provided with a site start-up packet. The start-up packet should include the final protocol, investigators brochure, a draft budget, draft contract, all the required regulatory documents, and instructions for how the sponsor wants you to fill out and return them. Please reference Fig. 2.3 for an average timeline of the start-up process.

Inset 2.6

- Contract Research Organization (CRO): As the term implies, this is a groupe hired or contracted out by the Sponsor to administer the trial. Clinical trials are often the most expensive part of investigational research. To successfully usher an investigational product from the clinical phase to the marketing phase can require hundreds of research sites, thousands of study volunteers, and millions or billions of dollars. To save money, and to have a relatively fixed handle on the cost of each phase of a trial, a sponsor may hire a CRO or Academic Clinical Trials Unit (ACTU) to administer a study. A CRO may also have a niche, such as dermatology (e.g., DermTech), and provide resources and expertise to a smaller pharmaceutical company that may not have the staff to dedicate to trial administration. Working with a CRO can provide you with access to a study and help you build your portfolio of clinical research. The drawback to working with a CRO is that administrative fees taken by a CRO amount to a "tax" on your revenue.
- Site Management Organization (SMO): An SMO is essentially a CRO, but one that is affiliated with a site, such as a hospital or academic institution. If you are in private practice and work with an SMO, you have to make sure your contract has legal protections for you regarding intellectual property, Anti Kickback Statutes, and Stark Laws. Site management organization, manages a number of sites in its network. SMOs are also proliferating internationally, where costs are less, but where oversight is also more difficult.

Fig. 2.3 Timeline of study initiation for academic centers that may be utilizing local Institutional Review Boards (IRB). Note, the time course listed is a rough estimate. Actual times may vary depending on institution and whether or not a local or central IRB is used

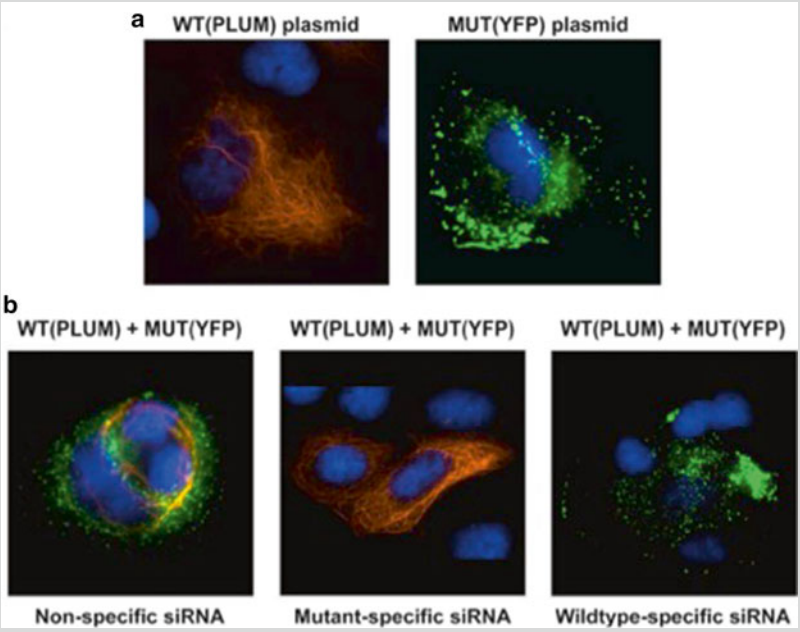
Inset 2.7

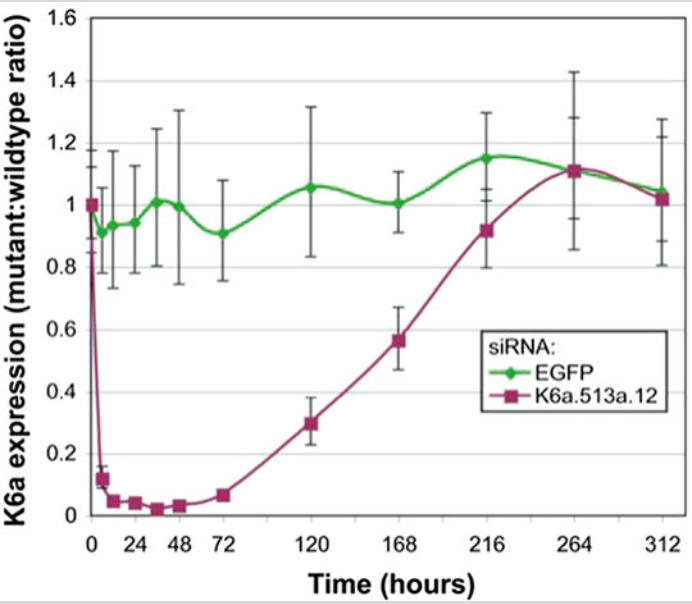
A listing of clinical trials can be found at the following web site: www.clinicaltrials.gov. An example of a pilot study on a rare genodermatosis using siRNA is a study of TD101:http://www.clinicaltrials.gov/show/NCT00716014.

This is a first in humans Phase I dose-escalation trial of an interfering RNA in a dominant negative genodermatosis.

Sancy A Leachman, Robyn P Hickerson, Mary E Schwartz, Emily E Bullough, Stephen L Hutcherson, Kenneth M Boucher, C David Hansen, Mark J Eliason, G Susan Srivatsa, Douglas J Kornbrust, Frances JD Smith, WH Irwin McLean, Leonard M Milstone, Roger L Kaspar. First-in-human Mutation-targeted siRNA Phase Ib Trial of an Inherited Skin Disorder. Mol Ther. 2010 February; 18(2): 442–446.

In vitro studies show dominant interference of keratin filament function.

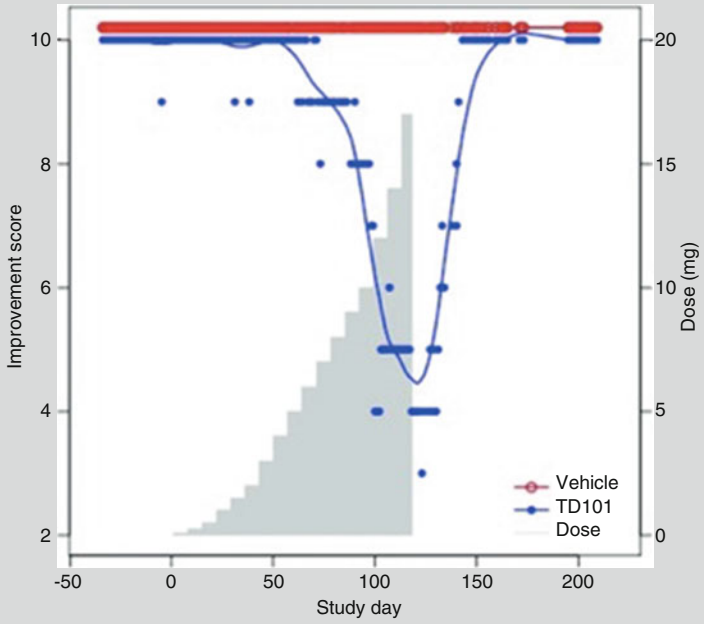




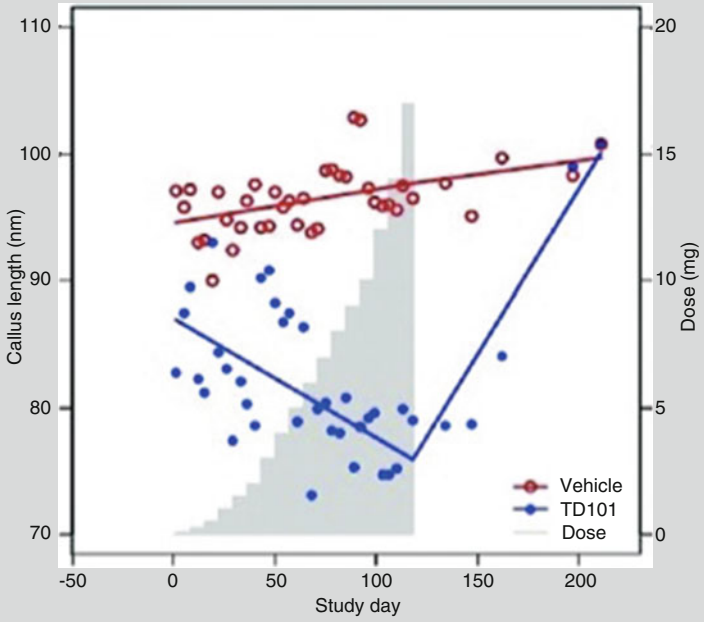
Dose of administered siRNA injected into subject lesions was escalated over 119 days, to a maximal concentration of 8.5 mg/mL and a total dose of 17 mg.

Week	Dose no.	Days	Volume (ml)	Concentration of TD101 (mg/ml)	Total dose TD101 (mg)
1	1-2	1-7	0.1	1.0	0.10
2	3-4	8-14	0.25	1.0	0.25
3	5-6	15-21	0.50	1.0	0.50
4	7-8	22-28	1.0	1.0	1.0
5	9-10	29-35	1.5	1.0	1.5
6	11-12	36-42	2.0	1.0	2.0
7	13-14	43-49	2.0	1.5	3.0
8	15-16	50-56	2.0	2.0	4.0
9	17-18	57-63	2.0	2.5	5.0
10	19-20	64-70	2.0	3.0	6.0
11	21-22	71-77	2.0	3.5	7.0
12	23-24	78-84	2.0	4.0	8.0
13	25-26	85-91	2.0	4.5	9.0
14	27-28	92-98	2.0	5.0	10.0
15	29-30	99-105	2.0	6.0	12.0
16	31-32	106-112	2.0	7.0	14.0
17	33	113-119	2.0	8.5	17.0

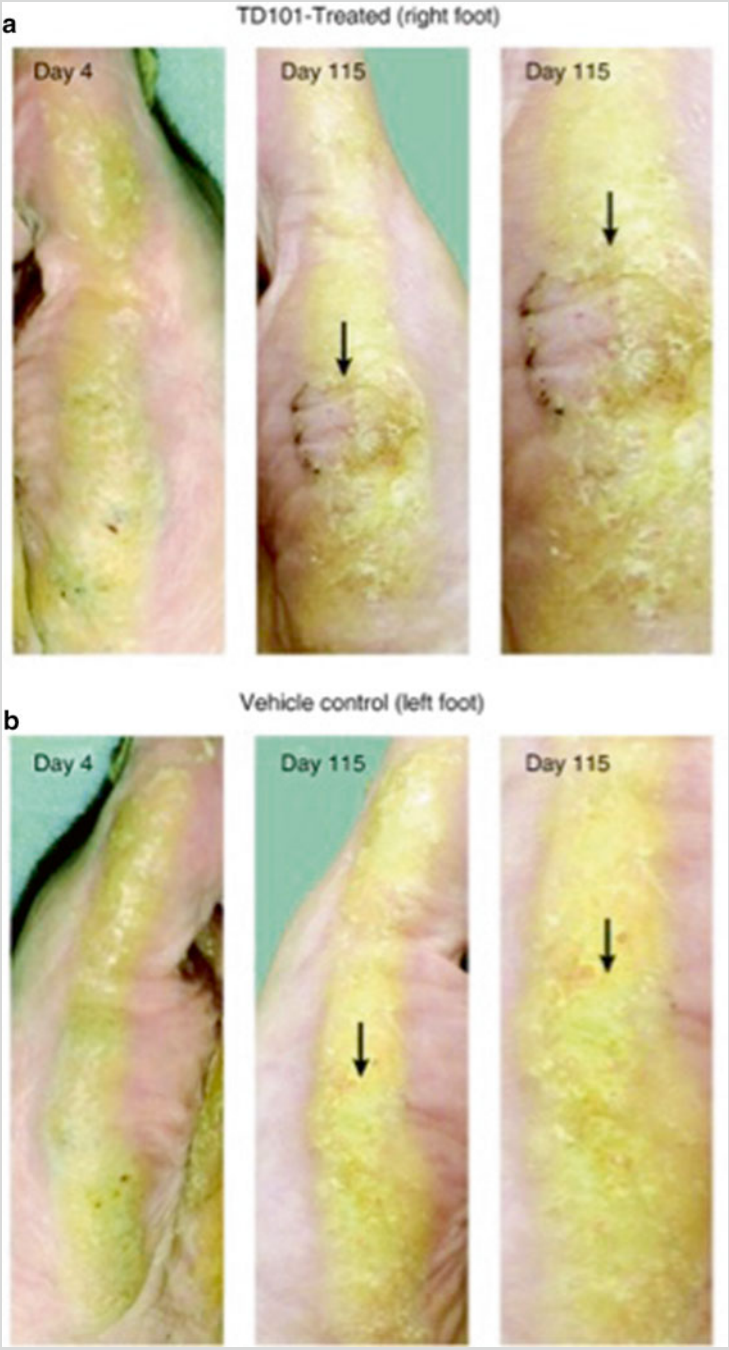
The patient assessed improvement of plantar skin thickness on the vehicle side and treated side.



Investigators measured callus thickness on treated and placebo surfaces.



Photographs were taken which prevented identification of the subject.



2.6.3 Site Equipment

For Industry-sponsored studies, the sponsor generally provides for protocol-specific equipment, including for lab collection, photography, incubators (to use for quantiferon gold testing), and even electrocardiogram machines. This is not always the case, however, and so purchasing a good high megapixel camera or even a microscope for KOH testing may be in order.

Any clinic or facility where lab testing is done, even if it is only a urine pregnancy test, is considered to be a laboratory under CLIA. A CLIA certificate of waiver must be obtained in order to perform any of the CLIA waived tests. More information about how this can be accomplished and which analytes are considered CLIA waived can be found on the CMS web page [29, 30].

2.6.4 Regulatory

The regulatory documents will include at a minimum the federal form 1572 and financial disclosure forms [31, 32]. These documents are the same across all studies and constitute an agreement between the Principal Investigator and the FDA that they understand the responsibilities of conducting a clinical trial and that they have disclosed any conflicts of interest (e.g. financial stakes). Sponsors will also collect signed and dated CVs and medical licenses for the Principal Investigator and all Sub-Investigators listed on the 1572. The instructions should tell you which forms require you to send off the original signed documents after making a copy for your files.

2.6.5 Institutional Review Board Submissions

Every site must get approval from an Institutional Review Board (IRB) or Ethics Committee (EC) before they can begin research at their site. Most institutional sites (University or Hospital affiliated) will require submission to a local IRB (specific to their institution) as opposed to a central IRB which is contracted by the Sponsor to review the study for approval for all other sites not affiliated with a local IRB. The sponsor/CRO will provide the documents required to complete a local IRB submission (i.e. draft informed consent documents, recruitment materials, patient diaries and questionnaires, or patient reported outcomes). For institutional sites with a local IRB, it is important to familiarize yourself with institutional policies and procedures as these may require multiple additional submissions for review (e.g. legal department or pharmacy services). A central IRB will require each site to register by completing an application or registration form (mostly an online process). The information required can include specific information about

the site, PI, and practices to ensure subject safety. The Central IRB submission process is simple and expedient for the site as the sponsor has already submitted the majority of the study documents on their behalf. Even the informed consent document is standardized across all the central IRB sites with the exception of the PI and site contact information.

The primary purpose of the IRB is to ensure the safety and welfare of the research subjects. In conjunction with the IRB application, either the sites or the sponsor will be required to submit any and all materials presented to potential research subjects and given to subjects during the study. Most importantly, the IRB will review the informed consent forms and ensure that the language is appropriate and can be understood by the target audience.

All research personnel should have appropriate ethics training and more sponsors are requiring that all personnel have ICH GCP training that is kept current as well [33]. Sites that can utilize the central IRBs have the advantage of a faster start-up time and therefore can usually start recruiting subjects earlier. Local IRB sites are responsible for submitting all documents to their IRB independently. This includes all modification and renewal documents as well. Studies will be required to submit a renewal submission prior to the expiration date every year. Most IRBs encourage submitting renewals 60–90 days in advance of the expiration date to ensure that the IRB has enough time to review any changes. At any point after the initial approval, a modification submission can be submitted for any changes in the proposed research. This includes (but is not limited to) changes to personnel, protocol amendments, new subject directed documents, or safety findings that may require updates to the informed consent documents. Consult your IRB coordinator or designated contact for clarifications on whether a required change needs to be submitted to the IRB. Usually, the answer is yes! Do not utilize new materials without submitting them to the IRB or confirming that they are IRB approved first.

2.6.6 Feasibility Continues with Budget and Contract Negotiations

The feasibility assessment does not end with the feasibility questionnaire and site selection. The successful investigator will be able to turn down a study that is not sufficiently funded. Before looking at the draft budget, the first step should be a methodical evaluation of the protocol, which should start with the schedule of assessments. Be sure to read the fine print found at the end of the schedule, which can clarify if certain procedures are required or only necessary under certain conditions. Special attention should be given to the procedures section of the protocol, which should clarify if personnel must have certain credentials to perform certain duties (i.e. efficacy assessments). The feasibility review can greatly impact the budget and scheduling constraints (e.g. Will the electrocardiogram (ECG) be reviewed by a cardiologist vs. another clinician?). Usually, these issues will be brought up at your site qualification visit, but some things get overlooked. Taking the extra time

to ensure that you have the appropriate patient population, staff, facilities, equipment, and expertise before you accept the proposal (i.e. sign on the dotted line) will help you avoid some of the most common errors that investigators make.

2.6.6.1 Budgeting

As with any budget, Industry-sponsored studies should be approached in an organized and methodical way. The contract negotiation process occurs at the same time as the budget negotiations and requires a keen eye and attention to details. A thorough review of the schedule of events can ensure that all procedure fees and assessments are being taken into account. From your feasibility assessment you know which staff members will be required to work on your study. Be sure to account for their time when conducting your budget review. Delineating PI/Sub-I time from SC time will allow you to better account for salary support. The schedule of assessments, the payment terms, and the draft budget should be reviewed together to ensure that all the line items match up. By developing a budget and payments checklist, you can be sure to account for all your costs. Do not just accept any payment terms. Pay attention to holdback percentage and final payment terms, monthly vs. quarterly payments, and screen failure terms. The difference can be in the details. Be sure to account for invoiced items like study start-up, IRB preparation for initial review, IRB amendment and renewal fees, document storage/archiving fees, and advertising costs. Some budgets may also require additional data entry fees, monitor visit fees, query resolution fees, and pharmacy fees. Be sure to take the extra time to evaluate the needs of each protocol. For particularly difficult-to-enroll studies, you may need to enlist the help of a recruitment coordinator and account for their time in the budget. You will have to ask yourself some hard questions here: Do you really have the time for this study? Can you afford to take this study given how much it may cost you in personnel time?

2.6.6.2 Contract and Payment Terms

Although not required, it is highly recommended that either a lawyer or someone with a legal background in corporate law review the contracts and payment terms. Institutional sites have a submission process for these documents to be reviewed by their legal department. For community practice sites, it is even more important for the PI to understand the terms of the agreement and be able to entrust someone who is trained on how to review and negotiate the terms.

2.6.6.3 Billing and Claims

It is becoming increasingly important for investigators to be up to date on the latest trends in regulatory and compliance matters. One such matter is conducting a Medicare coverage analysis to avoid unnecessary, and potentially very costly,

billing errors (i.e. false claims). This analysis determines routine costs which may be covered by Medicare or the patient's insurance vs. non-covered costs paid for by the study. This analysis is especially useful for studies that incorporate standard of care procedures/costs into the study. For many Industry-sponsored studies all the protocol-required procedures and assessments are covered by the sponsor and accounted for in the budget or contract, and therefore neither Medicare, the patient, nor their insurance should be billed. It should be clear from your review of the protocol, budget, and contract what all the potential costs are and who will pay for them.

2.7 Anti-kickback Statutes and Stark Law

Federal regulations strictly prohibit paying for or receiving inducements for patient referrals and further prohibit billing Medicare for services provided as a result of these referrals [34]. These laws are not limited to standard of care practices, but also extend to clinical research. Research subject referrals would also fall under the jurisdiction of these statutes. Therefore any kind of inducement or gift, whether monetary or other items of value, given or received for research subject referrals would also be prohibited. Research participants can, however, receive modest compensation for their participation in the study. The IRB/EC must approve compensation amounts to ensure that they are not coercive.

2.8 Working with CROs and SMOs

Working with a CRO or a site management organization (SMO) is standard practice in clinical research. With increasing regulations and tightening budgets, Sponsors (pharmaceutical companies) understand the importance of delegating the clinical research to groups with experience conducting and managing clinical trials. The CROs and SMOs are contracted to oversee and in some cases assume responsibility for certain duties as designated by the Sponsor or clinical investigator. These duties can include (but are not limited to) study management, negotiating contracts and budgets, site selection, data management, recruitment of study subjects, and evaluation of safety events (AEs and SAEs). Working with the middle man can inevitably cause delays in response times and the occupational hazard of working with a lot of people with very specialized roles. Generally, however, the standardization of the clinical research process across the industry tends to streamline the process. The same regulatory documents and general IRB submission processes are set in place for all studies. The difference is in the details and knowing the regulations (i.e. ICH GCPs and Code of Federal Regulations) [33, 35].

2.8.1 *Institutional/Academic Sites vs. Community Practice Sites*

Both institutional sites and community practice sites have their own advantages. Institutional sites can usually conduct studies with more intensive protocols (e.g. multiple blood draws over many hours, inpatient/overnight stays, specialized equipment/lab procedures). Some protocols require audiology, ophthalmologic testing, DEXA scans, specialized ELISA testing, or corneometry assessments. Institutional sites may be more likely to see rare or less common skin conditions (e.g. Hidradenitis Suppurativa and Epidermolysis Bullosa). Community sites, on the other hand, tend to have quicker start-up times, can utilize central IRBs, and the overhead/F&A costs at community sites tend to be lower than at Institutional sites. For high enrolling studies looking for subjects with more prevalent conditions (e.g. Psoriasis, acne, onychomycosis) community sites are more attractive.

2.9 Advantages of Training in Clinical Trials

There is a projected shortage of clinical trial investigators that has been attributed to several reasons [27, 36–38]:

1. Fewer medical students becoming M.D.-Ph.D.'s (physician scientists)
2. Decreased NIH funding
3. Lack of training in clinical research
4. Increased regulation and monitoring of clinical trials
5. Scarcity of mentors
6. Lack of adequate time for research

These factors are causing the pharmaceutical industries to look to private practices and sites outside the United States that can help them reach the goal of fast recruitment and enrollment. This could be a challenge but also an opportunity for physicians interested in becoming a PI. These are some of the advantages of becoming a clinical trials principal investigator (PI) [27, 39]:

Professional

- Allows you to remain on the cutting edge of a specific area of medicine
- Makes you knowledgeable of the new mechanisms of action, drugs available before anyone else
- Increases your professional recognition as an expert in the field
- Helps advance your academic career and promotions
- Adds prestige to your practice or institution
- Gives you the opportunity to meet, network, and collaborate with other experts in the field to promote new ideas
- Some PIs may be selected to contribute as co-authors for publications

Personal

- Personal satisfaction of giving more alternatives to your patients
- Seeing new drugs on the market that you helped get there
- Having a role in the advancement of medicine in your particular field
- Increased compensation

Patients

- Patients have early access to drugs that may be beneficial to them, increasing their options of treatment.
- Patients have the opportunity of receiving treatment at no cost for them, in a very controlled and safe environment.

Society

- The ultimate goal of clinical research is to benefit society by offering new information about the diseases or treatments.

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Useful Links

US Food and Drug Administration (FDA): www.fda.gov
Clinical Trials.gov: www.clinicaltrials.gov
Good Clinical Practices: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf
Association of Clinical Research Professionals (ACRP): www.acrpnet.org
Society of Clinical Research Associates (SOCRA): http://www.socra.org/
Model Agreements & Guidelines international (MAGI): http://www.magiworld.org; http://magiworld.org/standards/MAGI_Model_CTA_Abbreviated.pdf
Example of a blank 1572 form: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf
Training: http://www.fda.gov/Training/default.htm
Collaborative Institutional Training Initiative (CITI): https://www.citiprogram.org/
NIH Office of Extramural Research: http://phrp.nihtraining.com/users/login.php
Harvard Catalyst Master's Program in Clinical and Translational Investigation: http://catalyst.harvard.edu/services/mpcti/
NYU Langone Clinical and Translational Science Institute: http://ctsi.med.nyu.edu/researcher-resources/training-and-education/degree-programs/msci/
Food and Drug Administration Clinical Investigator Training Course: http://www.fda.gov/Training/ClinicalInvestigatorTrainingCourse/default.htm
Translational Biotechnology Fellowship at Galderma: http://www.aad.org/education/awards-grants-and-scholarships/translational-biotechnology-fellowship
Example of a Clinical Trial Agreement: http://www.iom.edu/~/media/Files/Activity%20Files/Research/DrugForum/April27–28/TemplateCTA%2042209.ashx.

Chapter 3
Dermatologic Clinical Trials: A Practical Approach

Shalini V. Mohan and Anne Lynn S. Chang

3.1 Introduction

This chapter is written for dermatologists who want to learn about practical aspects of clinical trials. It is a practical overview of the clinical trials setup and conduct process in the academic research setting. Given the complexity and scope of clinical trials, this chapter is not comprehensive but provides an initial framework for further reading.

One of the key distinctions for all physicians who conduct research on human subjects is between clinical "practice" and "research." Research-related activities pertain to those that test a hypothesis and therefore contribute to generalizable knowledge. Participation in a research study may help determine if a treatment is safe and effective. Hence, unlike dermatologic practice where the intent is to enhance a patient's well-being, dermatologic research may not lead to any benefit for the participant. Clear boundaries need to be identified that minimize any potential harm for study participants.

3.2 Aspects of Clinical Trials "Unique" to Dermatology

There are several aspects of clinical trials that are "unique" to dermatology. As the skin is a visible and accessible organ, the following points are more likely to apply in dermatology than in other fields of medicine:

- The study agent may be delivered topically (such as ointments, creams, gels, foams, or dressings). Instead of counting oral capsules or tablets in a bottle to

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assess study drug usage, the tubes containing the topical agents can be weighed at study visits to ascertain study drug usage.
- Since the skin is usually visible to the study participant, irritation reactions or responses to study agents may be more difficult to blind.
- Photographs are a good way to document skin changes over time, enabling independent, blinded review such as in skin cancer trials.
- Several tools are unique to dermatology to quantitate skin findings. Examples include transparent grids to trace the shape and size of ulcerations, validated and reproducible scoring systems for chronic skin conditions such as the Psoriasis Area Severity Index (PASI) for psoriasis.
- Since the skin is accessible to biopsy, tissue sampling can be performed over time, such as before, during, or after a study drug or treatment. There is also a spatial specificity to the biopsy, for instance, an untreated area of skin may be biopsied and compared to treated areas, thus enabling study participants to serve as their own controls.

3.3 Study Design and Protocol Development

An investigator-initiated clinical trial usually starts with an interest in answering a clinically relevant question. Biostatistical consultation is critical to establish the most appropriate study design to answer a research question. Biostatistical consultation will help to estimate the sample size needed to achieve sufficient power to answer a research question. If a single institution is unlikely to recruit a sufficient sample size, the study may need to involve multiple institutions, particularly if the disease under study has a low incidence or prevalence.

The gold standard study design is the double blind, randomized, placebo-controlled trial. This design has the least potential for bias from the researcher and participant; however, this may not always be feasible due to limitations in sample size and financial resources. Other study designs include crossover design, in which subjects serve as their own controls, and open-label studies, in which all subjects receive the study drug.

After the study design has been determined, the process of developing the protocol involves multiple revisions as information is acquired. For drug studies, elements of the protocol include an introduction section providing a broad overview of the disease being studied, including background information (such as basic mechanisms of disease or drug action), current treatment options, and gaps in treatment. Preclinical data on the drug being studied should be summarized, with references. Any existing clinical data, whether published or not, should be included. The clinical data may include early phase clinical trial data that may be unpublished that would include pharmacodynamics and pharmacokinetic information and dose limiting toxicities. For investigational agents that are not yet commercially available, working closely with industry partners is critical for access to up-to-date information on a particular drug. Differences between academic and noninstitutional/nonacademic trials are discussed later in this chapter.

The protocol should have a section on the rationale of the study, and the primary and secondary objectives of the study. The protocol includes a description of the study design, patient population, and inclusion and exclusion criteria. The visit schedule, efficacy assessments, safety assessments, and assessments of treatment compliance should be outlined, each in their own separate sections. Questionnaires for the participant to fill out may be utilized to capture subjective data such as quality of life issues, and survey items may be modeled after validated questions from the existing literature. A study calendar of the study visits and required procedures for each visit is invaluable to summarize the protocol and makes for easy reference.

Additional information that is included in the protocol includes how the study drug is supplied, how the study drug should be stored and prepared, and how the study drug is to be disposed or destroyed.

A data management section outlines how the data is to be collected, first via source documents and then entered into case report forms. Plans for handling missing data points should be defined. The statistical tests to be used in the analysis should be delineated in the protocol [1–3].

3.4 Institutional Review Board Submission and Approval

Once the protocol is finalized, it should be submitted to the local human subjects ethics board, or Institutional Review Board (IRB), for approval (Fig. 3.1). Dermatologists not affiliated with academic institutions may utilize commercial/private ethics boards. The detailed protocol is included in the IRB submission and specific questions from the IRB need to be answered. These include how the informed consent process will be performed, procedures to minimize risk to the study participants including potential loss of confidentiality, and all study-related procedures and their risks to the participants.

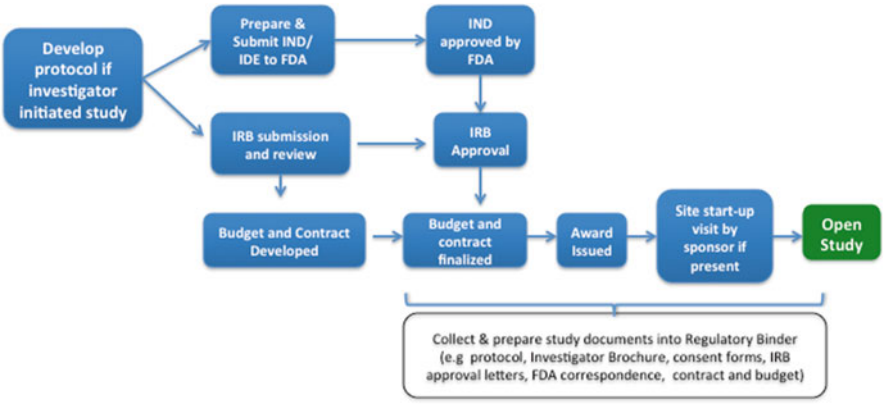

Fig. 3.1 Overview of clinical trial setup in the academic setting. Diagram showing the workflow for initiation, submissions and approvals needed for a clinical trial

After IRB review, there may be queries that must be addressed prior to approval. In some cases, the protocol may need to be modified based on IRB recommendations. One of the critical components of the protocol is the informed consent form, which should be written in lay language, and clearly state the purpose of the research study. In addition, the informed consent form should include study-related procedures, risks and benefits of study participation, any costs to the participant and the human subjects' rights (including the right to withdraw from the study at any time). The informed consent form may need to be amended as new information on the risks or benefits of a study drug become available. Adequate time to read the consent form and ask questions should be given. The informed consent form is signed by the potential study participant (or legally authorized representative) and a trained research staff member. If the potential participant is under 18 years of age, a parent or guardian signs the informed consent form, and the minor signs an assent form, if they are able.

3.5 Investigational New Drug Application

The United States Food and Drug Administration website (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm) provides a guide of whether human research studies require an investigational new drug application (IND). A study may be exempt from IND application if it is lawfully marketed in the USA, is not intended to support significant change in labeling or advertising of a drug and is not administered in a different route than the currently approved one (such as topical to oral administration) [4].

3.5.1 Drug Versus Device Trials

The FDA considers a drug a product whose primary intended use is "achieved through chemical action" whereas a device is a product used as an instrument or apparatus for prevention, diagnosis, treatment. For dermatology, these include dressings, adhesives for superficial skin lacerations, negative pressure wound therapy, and suture material. The safety and effectiveness of a device can be tested in a clinical trial. If the device is a significant risk to study participants, an "investigational device exemption" (IDE) can be submitted to the FDA. The device is classified by level of risk. IDE pre-submission meetings with the FDA to identify the type of scientific evidence needed for approval can be arranged. This can include clinical trial design and scope. Prior to commencement of a clinical trial, device studies require IRB approval as well as IDE exemption approval [5]. Subsequently, devices that are novel or have significant risk can be submitted to the FDA for a Premarketing Application (PMA) through clinical trials to approve a device for an intended use.

3.6 Budget and Contract Development

Once a protocol is finalized, a budget for the study can be estimated. At academic institutions this involves close collaboration with a budget development office where pre-determined prices for procedures and supplies can be obtained. Budget considerations include the amount of time allocated for a particular study, number and type of staff needed (e.g., biostatistician, research coordinator), cost of study agents, cost of clinic rooms, cost of supplies such as skin biopsy kits, cost of monitoring the study, and IRB costs.

For studies that involve industry partners, contract development with the legal team representing both the industry partner and the academic institution must be in place prior to study start. Elements of the contract include budget, indemnification (responsibility for any lawsuits or claims as a result of the clinical trial), and study duration.

3.7 Regulatory Issues

Regulatory issues pertain to compliance with government requirements for clinical trials. Documentation of measures taken to comply with regulations are compiled in a "regulatory binder." The regulatory binder serves as a repository for study documents and includes the following elements: FDA 1572 (Statement of the Investigator), IRB approval letters and correspondence, signature and delegation log of all study staff, screening and enrollment lists, all versions of protocol and investigator brochures, all correspondence with industry sponsor and FDA, curriculum vitae of all study staff and their required training, list of protocol deviations and associated memoranda detailing the deviations, reportable serious adverse events (SAE), certificates of accreditation from clinical laboratories, specimen logs, copy of normal ranges of laboratory values. A helpful way to organize these sections would be to place the commonly used items towards the beginning. The regulatory binder is continuously updated during the course of the study [1–3].

3.8 Study Start-Up

The contract agreement needs to be finalized and routes for billing study costs established. Institutional account numbers need to be set up for the study. All required regulatory documents should be in place, including an IRB approval letter and consent forms that have not expired. All source documentation should be created with checklists for all procedures associated with study visits (Fig. 3.2). Case report forms to capture the critical data points should be in place. Study drug availability and dispensing should be confirmed from the investigational pharmacy prior to study start.

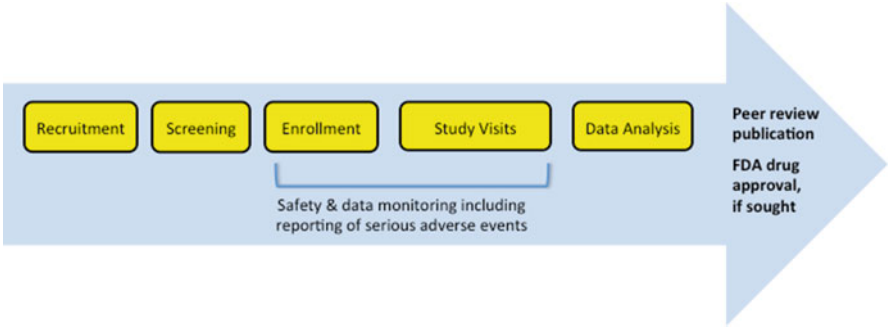

Fig. 3.2 Schematic of clinical trial conduct. Overview of clinical trial conduct from patient recruitment to publication and/or new drug development

All study staff need to be familiar with the protocol and have a chance to ask questions if anything is unclear. Industry-sponsored studies usually have a site initiation visit or meeting to review the protocol and answer questions.

Clinical trials that are interventional in nature and involve drugs or devices must be listed on the publicly available national website (www.clinicaltrials.gov). This is a searchable database for health care providers, patients and their caregivers to find studies that might be appropriate for a particular dermatologic condition. The studies are regularly updated, including information on whether active recruitment or enrollment is occurring, the inclusion and exclusion criteria, locations of centers where the study is being conducted, and results of the study when they become available.

3.9 Recruitment

Recruitment for appropriate subjects may occur in a number of ways and depends on the type of subjects who might have a disease or condition being studied. For trials seeking healthy volunteers or participants with common dermatologic conditions, IRB approved newspaper or Internet advertisements may be appropriate. Paper postings on community boards or paper advertisements left in waiting rooms of clinics can be effective in recruiting study subjects. For more rare diseases, participants may be recruited through referrals from other physicians, including community physicians or other health care providers or through patient support groups.

3.10 Screening

Pre-screening in the form of a telephone interview is a good way to save time for both the potential participant and research study staff. The telephone interview follows a pre-determined script approved by the IRB, which includes the purpose of

the study, a brief description of the study procedures, and inclusion/exclusion criteria. Once the pre-screening process identifies a potential participant, they can be invited for a screening visit. There may be the option of destroying identifying information if the potential participant does not wish to participate or does not qualify for the study.

Prior to all study-related procedures, written informed consent is obtained when the potential participant present for study screening. As described above, the written informed consent form includes the purpose of the study, all study-related procedures, risks and benefits of participation, research subjects' rights, and contact information for the ethics board and study staff. The informed consent form should be written in layman's terms. The potential participant should have adequate time to read the consent form and ask questions. In some cases, the potential participant may want to take the consent form home to discuss with family members. If potential participants cannot read English (or other language that the consent form is in), or are hearing impaired, an interpreter may assist with reading the consent form and facilitating question and answers. The procedures for participants who cannot read English can vary from institution to institution. Children who participate in clinical trials may be asked to sign an Assent form, with their parent, guardian, or other legally authorized representative providing written informed consent. Potential participants who are unable to summarize the contents of the informed consent form or ask appropriate questions may be decisionally impaired and unable to sign the informed consent form.

After informed consent is obtained, study-related procedures such as medical histories, physical examinations, laboratory or radiographic examinations may be obtained. These pieces of information will determine whether a participant meets the inclusion and exclusion criteria of the study. Participants who do not meet the inclusion and exclusion criteria are deemed "screen failures." They may be re-screened if their circumstances change and they would like to join the study at a later date [1–3].

3.11 Enrollment

Participants who provide written informed consent and meet all inclusion and exclusion criteria may be enrolled into the clinical trial. The enrollment visit may occur on the same day as the baseline visit, or it can be a separate day. If there is a randomization component to the study intervention, it usually occurs on this day. Baseline assessments of disease severity are performed and questionnaires for subjective data may be administered. For drug trials, participants usually receive their study agents with instructions on how to take the study agent. Typically, a study diary is given to the participant to assist in accurate dosing and to account for any missed doses of study agent. The diary is also a good way to track any side effects during the study, regardless of whether they are related to the study agent.

3.12 Study Visits

The timing of the study visits follows the study calendar outlined in the protocol. Checklists can facilitate the completion of all study-related procedures for every visit. The visit usually includes inquiring about adverse events (whether they are related to the study agent or not) and any changes in medication since last visit. Study agent is collected, logged, and compared to patient diaries. Any discrepancies should be noted, and checked with the participant. If a previous informed consent form has expired and/or replaced by an updated version, the participant and investigator should review and sign the most recent informed consent form. If the patient is to continue in the study, the next visit can be set up so that the timing corresponds to study calendar requirements.

3.13 Safety and Data Monitoring

Safety is followed in a number of ways. This includes assessment of adverse events reported by the participant and any laboratory values that are outside the range of normal. The laboratory tests that are followed during the study depend on the known side effects of the study agent. In addition, participants who do not comply with study-related procedures may pose a safety risk, and may be discontinued from the study at the investigator's discretion.

Serious adverse events need to be reported to the IRB, the FDA, and the study sponsor (if there is one). In general, prompt reporting to the IRB is required if (1) an unanticipated problem occurs that is also (2) related to research participation, and (3) places the research participant at increased risk of harm (including physical harm, loss of confidentiality, psychosocial distress). Other circumstances that require IRB reporting include new information that alters the risk or potential benefits of the research and deviation of the protocol, especially if it was harmful to the participant. Adverse events that are not serious may not need to be reported immediately to the IRB, but can await annual continuing review.

Data monitoring is generally performed a few times during the course of the study. The monitor may be an independent consultant retained for the study in investigator-initiated studies, or be provided by the study sponsor. Data monitoring may occur after enrollment of the first participants to check whether study procedures are being correctly followed and to avoid future errors. It may also occur after a certain number of patients have been enrolled, such as the first ten patients. At the conclusion of the last visit of the last patient, monitoring will help to ensure that all the data is present and to resolve any discrepancies between the protocol, source documents, and case report forms. At that point, the data may be "locked" for analysis. The monitor will also check that the regulatory binder is maintained and up-to-date [1–3].

3.14 Data Analysis

Using the data captured in the case report forms, the statistical analyses addressing the primary and secondary objectives are carried out. These objectives often pertain to efficacy of the study drug and frequency of side effects. In general, intention-to-treat analysis is carried out so that all patients who enter the study are included in the analysis. For patients that do not complete the study, the last data point prior to study discontinuation can be used.

Final study reports or manuscripts usually include (1) a flow chart depicting screening, enrollment, screen fails, study dropouts, (2) a table of participant demographics, and (3) tables and figures that depict the results. The Consolidated Standards of Reporting Trials (CONSORT) checklist to promote transparency in reporting of randomized clinical trials is a helpful outline to utilize. The final report and/or manuscript should interpret the results and place the results in the appropriate medical context.

3.15 Peer Review Publication

The results of the data analysis can be submitted for publication in a journal so that they will be accessible to physicians, researchers, and patients. Inclusion of a study usually requires manuscript review by peers who are familiar with the research topic and methods. These peer reviewers may raise concerns about how the data was collected or how the data was interpreted. These issues typically have to be considered and addressed before the study is accepted for publication.

3.16 New Drug Application

The results from a clinical trial can be used to design future larger studies, such as phase 3 clinical trials. If the clinical data is being used to support FDA approval for a particular indication, the clinical data needs to show that the drug is safe and effective for the proposed use. The FDA application form for drug approval in the USA is the New Drug Application (NDA). In addition to clinical efficacy and safety, other information included in the NDA are results of animal studies, pharmacokinetics and pharmacodynamics, manufacturing, processing, and packaging. Drugs are typically approved by the FDA for a particular indication after phase 3 clinical trials, although in some cases, approval may occur after phase 2 studies [6].

3.17 Clinical Trial Settings: Academic Versus Nonacademic

The general purpose of clinical studies performed in the academic setting is to contribute new knowledge in dermatology, whereas most studies in the nonacademic setting are related to developing a drug or device for commercial use. There is certainly overlap, in that academic investigators partner with industry collaborators to access new drugs, and industry may call on the expertise of academic investigators in designing studies or exploring uses of existing drugs or devices. For example, alpha agonists have been shown to reduce cutaneous erythema when used topically, a finding that could be determined in the academic setting using pre-existing drugs that were commercially available. The publication of these findings could lead to "off-label" usage of the drug in the clinical setting. While nonacademic studies may provide support for academic investigators to study off-label use of pre-existing products, often the studies conducted by industry are for the purpose of obtaining FDA approval for a new drug or drug indication [7].

Several groups have examined outcomes of clinical trials performed in different enrollment settings. For instance, in cancer trials, variations in patient attributes (e.g., age, ethnicity, sex, and disease severity) were found, but there was no significant difference in mortality outcomes [8]. Because of these variations, many clinical trials will include both academic and nonacademic settings.

3.18 Final Comments

Many aspects of dermatologic clinical trials are too complex to be addressed in this short format. Examples include how to obtain funding for clinical trials, issues of financial conflict of interest on the part of the investigators, details of Good Clinical Practices, and how to handle collaborations across multiple institutions. We have provided a number of references for additional reading on this topic, below. Many individuals in the field such as clinical research coordinators obtain on-the-job training working under an experienced clinician familiar with clinical trials. Additional resources for clinical trials training include coursework either at professional meetings or community colleges. Finally, no two clinical trials are exactly alike, as the purpose, procedures, and the trial participants are never the same. By nature, research involves asking new questions and acquiring new information; thus, using good judgment to adapt to new scenarios within the framework of regulatory requirements and good clinical practices is absolutely critical.

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Further Readings

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Chapter 4
Device Clinical Trials

Todd E. Schlesinger

Conducting clinical trials can be a rewarding experience for the practicing physician, but they are also a lot of hard work. This chapter aims to provide a practical overview for those of you who may be interested in performing office-based clinical trials. Introductions will be made into the background of clinical trials, types of sites conducting trials, people conducting those trials, what may be needed at your location, regulatory information and a practical how-to guide to getting started doing your own studies.

4.1 What Are Clinical Trials?

Clinical trials are studies involving human subjects that are conducted to evaluate the feasibility, safety, efficacy, and long-term effects of medications, devices, treatments, or procedures. In the USA, trials are often organized and paid for by companies seeking approval from the Food and Drug Administration (FDA) to market and sell their treatment to health care providers and/or patients. The FDA is responsible for the approval of all studies involving new medications, devices, and treatments and has set forth a step-wise process that studies must go through before receiving permission to sell their product. All clinical research studies are conducted according to a plan or protocol that must be followed during the study. Deviations from the protocol are documented and managed over the life of the study.

Clinical research studies are classified into two main types. The observational study allows investigators to evaluate health outcomes without subjects being assigned to particular interventions. However, observational studies suffer from

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A. Nasir (ed.), *Clinical Dermatology Trials 101: A Primer for Dermatologists*,
DOI 10.1007/978-3-319-09027-6_4

their reduced ability to provide causal evidence as can a properly designed interventional study. In a cohort or panel study, a group of patients is closely monitored over a span of time. An example of this type of study is the Psoriasis Longitudinal Assessment and Registry (PSOLAR), which is an observational, prospective, cohort registry designed to track the safety and outcomes of patients with plaque and other types of psoriasis over time [1]. In a case control observational study, two different groups are observed. The case group will have a particular condition and the control group will not. Cases and controls will be otherwise matched as closely as possible and both groups will be observed for the prevalence of a potential other condition, which the authors may feel is related to the condition selected for the cases. An example of a case control trial in dermatology can be found in a study in which age, hair color, and family history of melanoma-matched groups were assessed for their level of vitamin D intake using a food-frequency questionnaire to determine whether vitamin D intake had a protective effect against melanoma [2]. Cross-sectional trials are those observational trials that collect data on a population or subset of a population at one specific point in time. Cross-sectional trials differ from longitudinal trials, in which observations are made more than once over a period of time. For example, a cross-sectional study was conducted to evaluate differences between rosacea subtypes in epidemiological associations and clinical features. In this study, subjects were evaluated for rosacea subtype by a dermatologist and surveyed for demographics, onset of signs and symptoms and progression of disease between subtypes [3]. Retrospective studies look backwards to try and make useful correlations between various conditions, disease states, treatments, or outcomes. For example, in a large retrospective study, Dr. Alexa Kimball, a professor of dermatology at Harvard Medical School, was looking, among other things, to estimate the 10-year risks of coronary artery disease and stroke in patients with moderate to severe psoriasis. A large amount of data was pooled from subjects already enrolled in phase II and phase III clinical trials and compared with that of the general population [4].

The interventional study also known as a clinical trial calls for subjects to be assigned particular treatments, the outcomes of which are evaluated according to the protocol. Pilot studies, also known as proof of concept studies, are undertaken on a small scale, typically to assess the feasibility of the approach that is intended for use in a larger size study. Playing a key role in the development or refinement of new interventions, assessments or other study procedures, results from pilot studies are commonly used to support more extensive and lengthier pivotal efficacy trials. Pilot studies may also provide an opportunity to develop consistent practices, train research staff and enhance data integrity. One caveat mentioned by Dr. Andrew Leon, in an article on the role of pilot studies in clinical research, is that investigators should be "forthright in stating these objectives of a pilot study and bravely accept the limitations of a pilot study. Grant reviewers should accept no more [5]." Open label studies are those in which both the subject and the investigator are aware of which drug or device the subject is receiving. Single blinded studies typically are structured so the subjects are unaware of the treatment assignments. A powerful type of interventional trial is the randomized, double-blinded placebo-controlled trial. Neither the investigator nor the subject knows who is receiving the intervention

Table 4.1 Common types of clinical trials

Study type	Study design
Observational	• Cohort or panel
	• Case control
	• Cross-sectional
	• Longitudinal
	• Diagnostic
	• Retrospective
Interventional	• Pilot
	• Open label
	• Blinded, single or double
	• Randomized
	• Placebo controlled
	• Vehicle controlled
	• Crossover

or the placebo, nor will the study monitor and possibly those analyzing the data. Data obtained from this type of trial is the most reliable because a third party evaluates the results and bias is reduced. The blinded evaluator is not the same person who conducts study procedures or would have any knowledge of which subjects are in which arms of the trial. For example, a randomized, double-blind, vehicle-controlled study was undertaken to determine if topical combination therapy containing a retinoid and an antimicrobial was an effective treatment for acne vulgaris. In addition to the treatment arm, the study had additional arms for the individual ingredients used alone as well as an arm for vehicle [6]. In a crossover study, each subject will receive both treatments being compared, but at different points in time. Common types of observational and clinical trials are demonstrated in Table 4.1.

Before a new agent is studied in humans, it undergoes preclinical testing. During this phase, the primary aim of the sponsor is to use laboratory or computer-based modeling to determine the agent's action, metabolism, and glaring toxicities. The sponsor will want to be sure the agent will not expose people to excessive risk when evaluated in small, early stage clinical studies. The agent is also evaluated for potential commercial applications. Usually, the testing is conducted using mice or rats, then possibly in larger animals.

Clinical trials involving pharmaceuticals are classified by the FDA into four phases, organized by the position in the approval process the study falls into. Before a study can begin, an investigational new drug (IND) application must be submitted to the FDA and approved. The IND effectively makes the proposed drug "legal" for the purposes of conducting research leading to FDA approval for marketing. The sponsor (applicant) for an IND may be a drug manufacturer and/or marketer, or the investigator conducting the proposed clinical investigation. The IND application will contain information about the animal pharmacology and toxicity studies, information pertaining to how the drug will be manufactured and detailed protocols for proposed early stage studies. The sponsor must wait 30 calendar days after submission of the IND before conducting any clinical trials. During this time, the FDA will review the application to be sure the research subjects will not be exposed to unrea-

sonable risk and advise the sponsor if additional information or time is needed. Another type of IND is used for expanded access or "compassionate use." The expanded access IND requests approval to use an investigational drug outside of clinical trials to treat patients with serious or life-threatening conditions for which no alternative treatment exists.

Once approved, human trials may begin. Phase I involves a small number of subjects (5–100) and is designed to evaluate the initial safety, side effects, and dosing range of the new drug. Pharmacology (pharmacokinetics) and metabolism of the drug are also evaluated during this phase. Phase II trials are conducted by providing the drug to a larger number or subjects to check its effectiveness and continued safety. Phase III trials encompass giving the drug to large numbers of subjects and have the purpose of collecting additional safety information, comparing it to other available treatments and confirm its effectiveness. Information collected during this phase is used to evaluate if the drug can be used safely and is the basis upon which the FDA will decide whether or not to approve the drug. Phase IV studies are conducted after approval and after the drug has been marketed. During this phase, researchers learn how the drug effects various populations and may reveal side effects associated with long-term use [7].

Inset 4.1

The following trial is of a device, measuring safety only. This was a subject and rater-blinded trial of a microneedle roller device. The sham was reproduced by applying finger pressure. Subjects were treated on the forehead, nasolabial folds, and temples. Transient erythema which was self-limited was noted with use of the device compared to the control.

Safety of a novel microneedle device applied to facial skin: a subject- and rater-blinded, sham-controlled, randomized trial. Hoesly FJ, Borovicka J, Gordon J, Nardone B, Holbrook JS, Pace N, Ibrahim O, Bolotin D, Warycha M, Kwasny M, West D, Alam M. Arch Dermatol. 2012;148(6):711–7.

Device studies are handled somewhat differently. According to FDA regulation 21 CFR 807 Subpart E [8], a 510(k) or premarket notification (PMN) is required to be made to the FDA to demonstrate that the device is safe and effective. The 510(k) process also involves an evaluation of whether the device is substantially equivalent (SE) or non substantially equivalent (NSE) to another device already approved for marketing. Submissions are reviewed and processed by the Center for Devices and Radiological Health (CDRH) within the FDA. Within the CDRH, the Office of Device Evaluation (ODE) and the Office of In Vitro Diagnostics and Radiological Health (OIR) are responsible for clearance to market in the US. Reviewers consisting of field-specific engineers, physicians, chemists, and biologists among others determine if the device is SE or NSE. New devices must be classified according to FDA regulations into one of three classes known as Class I, II, and III, determined by the device's intended use, instructions for use, and risk-based assessment. Class I and II devices

are exempt in some cases from the PMN requirements and therefore do not require a 510(k) submission. All device classes are subject to a baseline set of requirements called General Controls as defined by the Food, Drug and Cosmetic Act (FD&C). Class I devices have a long and well-understood history of use and safety profile. Examples of Class I devices include manual surgical instruments, cotton gauze for external use, and wound hydrogels. Class II devices propose more risk than Class I devices and therefore are subject to additional controls such as guidance documents, special labeling, mandatory performance standards, and post-marketing surveillance in some cases. Examples of Class II devices include sutures, some lasers, intense pulsed light devices and some RF-generating devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Class III devices are subject to the PMN process and involves demonstrating SE to another legally US marketed device. Examples of Class III devices include injectable dermal fillers, most lasers used in dermatology practice, and wound dressings that contain human cells [9]. Section 515 of the FD&C Act, Chapter V: Drugs and devices contains information on the PMA process for devices that require it [10].

Inset 4.2

Drug and Device

Combination products (prefilled syringes, MDI, transdermal patches). These are a combination of a drug prepackaged in an administration device or delivery device. They are more difficult to make, and have more regulation to deal with, but can be safer. Examples include sirolimus-eluting coronary stents by J&J (CYPHER). Dermatology drug/device combinations include pre-mixed syringes for the delivery of biologic therapies for psoriasis, and canister/drug combinations for the delivery of foam-based topical formulations. Weather a combination product is reviewed by CDRH or CDER makes a big difference. The assignment is determined by the primary mode of action. Drug eluting stents are regulated as devices, but drug eluting disks for targeted chemotherapy are regulated as drugs.

This is an example of a Combination Device and Drug Trial conducted in multiple (28) centers in the USA and Canada:

Subjects were treated with varying doses of human fetal fibroblasts in this phase 2 double blind randomized placebo-controlled trial. They had leg ulcers 2–12 cm^2 in area lasting 6 weeks to 2 years. They were randomized in a 1:1:1:1:1 ratio with four escalating doses of cells or placebo. They were treated with compression bandages. All evaluators were masked during the study. The lower dose was found to be superior to vehicle in accelerating wound healing.

Kirsner RS, Marston WA, Snyder RJ, Lee TD, Cargill DI, Slade HB. Spray-applied cell therapy with human allogeneic fibroblasts and keratinocytes for the treatment of chronic venous leg ulcers: a phase 2, multicentre, double-blind, randomized, placebo-controlled trial. Lancet. 2012;380(9846):977–85.

4.2 Considerations Before Starting

So, what do you need to know before beginning a clinical trials program at your site? The first thing to know is that in order to conduct clinical research, personnel at your site must be trained in good clinical practices (GCP). GCP is an international standard for the designing, conducting, recording, and reporting of clinical trials that include the participation of human subjects. Derived from safety concerns arising in the 1960s, the World Health Organization developed guidelines to provide the public with a high level of confidence that the rights, safety, and health of trial subjects would be defended. The Declaration of Helsinki is a set of ethical principles developed by the World Medical Association (WMA) and is argued to be the gold standard in clinical trial ethics. Having undergone multiple revisions, since its inception, the Declaration of Helsinki is a living document that is in the public domain [11]. The International Conference on Harmonization (ICH) brings together regulatory authorities and the pharmaceutical industries from Europe, Japan, and the USA to promote harmonization among the groups. Additionally, there are two main government offices in the USA, the Office for Human Research Protection (OHRP) and the Office of Human Subjects Research (OHSR) that promulgate policies and procedures with respect to clinical trials. Compliance with regulations is fundamental to research practice. Free GCP training can be obtained by visiting the National Institute of Health (NIH) website at www.nih.gov [12].

Another challenge faced by prospective clinical investigators is determining and obtaining suitable training that will benefit them as they embark on a new and exciting professional opportunity. While a formal training program such as the Master of Science in Clinical Epidemiology Degree Program of the Perelman School of Medicine at the University of Pennsylvania [13] may be a good choice for someone with a desire for a career in academic medicine focused on research, those looking to add clinical research to an existing medical practice may wish to explore other options. Aside from degree-granting options, some clinical research programs offer abbreviated curricula for clinicians interested in pursuing clinical research, but may not have the time to undertake a 1 or 2-year degree [14]. Other options are presented by numerous professional organizations, which cite education as part of their mission. Examples include the Association of Clinical Research Professionals, the Society for Clinical Trials, and the Society of Clinical Research Associates which all may be found online. Some organizations offer certification programs as well as training for ancillary site staff.

Who will assist you in conducting your study? You, as the Principal Investigator (PI) are responsible for all aspects of your site's performance in conducting a trial [15]. Certain responsibilities as defined by the protocol may be delegated to site staff such as data entry, record keeping, and scheduling of subject visits. Busy sites typically have someone other than the PI who is responsible for the day-to-day management of the site. This person is often referred to as the Study Coordinator or Clinical Research Coordinator (CRC) and must be a detail-oriented person. It is important to have identified who on your staff will serve as your CRC before going out and trying to find your first study. Subinvestigators (SubI) are other physicians at the site who conduct patient assessments, but are not as involved with the administration of the

study as the PI. Depending on the size of the site as well as the number and type of studies being conducted, other personnel may be needed including a pharmacy technician, medical assistant, and office manager.

The sponsor is the pharmaceutical or device maker that is paying for and managing the trial. There will be certain personnel associated with the sponsor who will also assist your site in managing the trial. First is the study monitor or clinical research associate (CRA). CRAs visit the site on a regular basis and ensure the site is following the protocol and is responsible for ensuring proper data collection as well as documenting and reporting protocol deviations. Medical research associates (MRA) perform a role similar to that of the CRA, but are most commonly located at the sponsor's facility. Finally, the medical monitor (MM) is a physician who has the responsibility to answer protocol and study related questions. MM's are employed either directly by the sponsor or by a contract research organization (CRO) hired by the sponsor to manage the trial. Typically, they have study-specific knowledge and tend to have trained in the field in which the study is being conducted.

What are the physical requirements of your site? In the 1980s most clinical trials took place at universities or academic medical centers. By 2005, more than 70 % of US clinical trials were being done by nonacademic or private physicians. The number of private-sector physicians involved in studies increased from 4,000 in 1990 to 20,250 in 2010 [16]. In fact, this may represent the recognition of some of the advantages offered by private practice-based sites. Clinical trial capacity is the availability of patients to participate in trials. Subjects must also be motivated to be compliant and complete studies. Community-based sites may be better equipped to recruit and retain subjects than academic medical centers. Additionally, community-based practice is a vast untapped resource to increase research capacity [17].

Another consideration is the availability of an institutional review board (IRB) at your site. Under title 45 of the Code of Federal Regulations, IRB approval is required at each site participating in a study, including review of the proposed protocol and deciding on the need for informed consent [18]. An IRB is a committee made up of various members drawn from the scientific, ethical, legal, and public communities and is charged with approving each study from an ethical and safety standpoint. Each volunteer consent form is also reviewed for accuracy, ease of understanding and completeness. According to interviews with IRB personnel conducted by Dr. Robert Klitzman, a professor in the department of psychiatry and director of the master of science in bioethics program at Columbia University College of Physicians and Surgeons, IRBs face confusion and challenges with respect to finding, training, retaining, and the proper role of community IRB members [19].

According to an interesting review by Dr. Keith Marsolo, director of software development and data warehouse at Cincinnati Children's Hospital, there are three general categories that most IRBs fall into. Local IRBs are those housed at the same institution as the site and are typically found at academic medical centers, hospitals, research institutions, and universities. Challenges faced by sites governed by a local IRB may include unfamiliarity with the research proposed, stringent institutional guidelines and an extended turnaround time for responses and approvals. Central IRBs (CIRB), sometimes referred to as commercial IRBs are not tied to any specific institution and may focus on a particular area of research or geographic location.

Some may prefer the CIRB model as it often can provide a more focused approach, rapid response time, and easier access. The federated IRB model involves the combination of efforts of the local IRB and CIRB to facilitate efficiency and trust between institutions [20]. Determining the type of IRB your site can and will use is one of the first steps in preparing for soliciting your initial study as it is something that potential sponsors will want to know during the site selection process.

Lastly, I will say a few words about your site itself. One of the first steps in being evaluated by a potential sponsor is to undergo a site qualification survey (SQS). During this process, a potential suitor will evaluate whether your site is a good fit for the proposed study. Since the particular requirements will vary from study to study, suffice it to say that there are certain basic requirements that must be present for most research. Physical requirements include, but are not limited to, locked and temperature-controlled storage for study medication, secure storage for study materials, adequate facilities for conducting study visits, internet access for electronic data capture (EDC), access to fax, photocopy, telephone, and restrooms. Privacy issues will be assessed such as Health Insurance Portability and Accountability Act (HIPAA) compliance including physical and data security. There should be a comfortable space for the study monitor to use during his or her visits. Sponsors will also be looking to ensure you have adequate staff, interest and enthusiasm for the study and whether you are running competing studies. Subject recruitment and retention challenges will be identified and assessed. During this important process and potential visit, it is critical that the PI be available to show his or her affability and ability to conduct the research.

One of the pitfalls of beginning a clinical research program at your site is underestimating the time, work, and money involved in conducting studies. There may be significant delay when beginning a study before any payments are made to the site, so you must be prepared to cover the additional overhead incurred during this time. Research takes lots of time to prepare and conduct all the necessary steps. Be sure you are committed by doing a thorough analysis of your current practice and workflow before taking on your first project.

Awareness of reporting requirements for manufacturers can prepare potential investigators for disclosure as required by law. The Physician Payments Sunshine Act (Sunshine Act) also known as Open Payments, requires manufactures of drugs, medical devices, biologicals and supplies to report payment and transfer of value information to the Centers for Medicare and & Medicaid Services (CMS) on an annual basis [21].

4.3 Getting Your First Study

One of the easiest ways to get started in the world of office-based clinical research is to join an existing or new observational study or registry. Working with a registry type study can introduce you and your site to some of the routines encountered in many studies, but with less up-front costs and training. Since a registry does not involve study drug, there is no need to be concerned with drug storage, but secured

space for study documents will still be required. Most registries follow patients as they are being cared for in the course of normal routine, collecting data on treatment and outcomes. If you have a local IRB at your site, they may still have to approve the protocol, however, there will most likely be a uniform protocol for all sites. Registries are typically managed by a CRO and involve a CIRB.

Understanding the management structure of pharmaceutical companies can help you navigate within them, focusing your networking efforts on the right people in the firm that can help you land studies. Many sponsors have a research and development department under which there is a clinical development team further divided into phase I and phase II and III groups. These are the people responsible for conducting early phase and pre-approval clinical trials. On the other side is the medical affairs department. Medical affairs departments are often responsible for post-marketing (phase IV) studies and investigator initiated studies (IIS). Getting to know people in the medical affairs department at companies you are interested in working with can be fruitful. Start by asking pharmaceutical representatives that visit your office who your local medical science liaison (MSL) is and ask to meet with them. Prepare for the meeting by creating a one-page introduction letter describing your site. Include information pertaining to your patient population, demographics, patient base size, available staff, and your facility. Attach your curriculum vitae and be sure to include any publications you have coauthored and presentations you have given. If you have obtained GCP training, attach your certificate. During the meeting, ask about ongoing and upcoming studies and express your interest in becoming involved. Inquire if the company is seeking additional sites for an existing or new study. MSLs may speak about off-label indications and discuss products or devices in the pipeline that pharmaceutical representatives are not allowed to discuss. Due to increased regulation within the industry, most companies keep a healthy distance between the marketing department and the medical affairs department so as to avoid the perception of influence. Many companies have a site database that you will want to become registered in. During the site selection process, the database is the first place the clinical development department will look to find eligible sites.

Inset 4.3

This is a very small-scale pilot study of a novel indication—hidradenitis suppurativa—for an approved device based on a basic science understanding of skin biology and laser physics. A long-wavelength laser is expected to affect the follicular unit in the mid dermis, where much of the pathology for HS lies. Subjects with HS in this outpatient-controlled clinical and pathologic study were treated with two sessions of 1064 nm Nd:YAG laser therapy and evaluated at 1 week, 1 month, and 2 months after treatment with a modified lesion area and severity scale. A significant drop in HS severity was noted, and fibrosis of the dermis was seen.

Xu LY, Wright DR, Mahmoud BH, Ozog DM, Mehregan DA, Hamzavi IH. Histopathologic study of hidradenitis suppurativa following long-pulsed 1064-nm Nd:YAG laser treatment. Arch Dermatol. 2011;147(1):21–8.

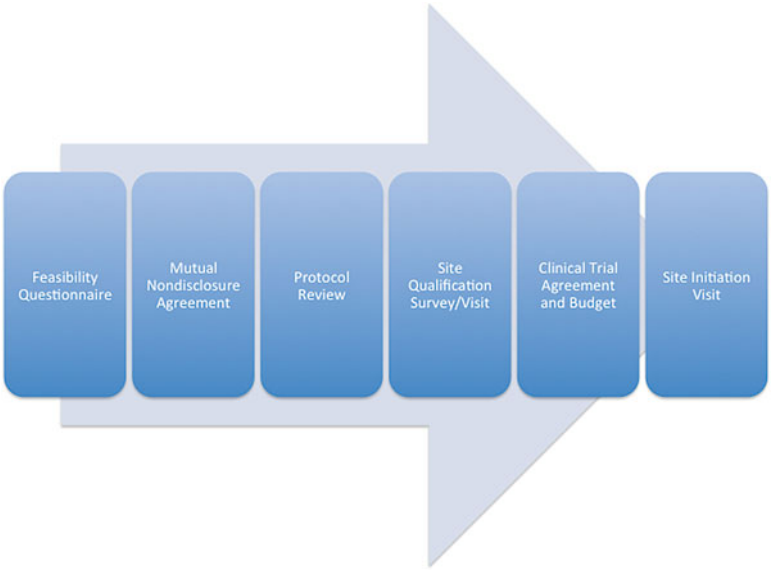

Fig. 4.1 Steps leading to beginning a study

Getting meetings with MSLs in some companies can be challenging. The larger the company, the harder it is to identify the decision makers. One tip to get the process rolling is to engage in a game of "speed dating." Start by identifying a national or regional educational meeting in your specialty that you will be able to attend. Plan to bring your CRC along to help divide and conquer. Use the meeting program, looking to the list of sponsors and/or exhibitors. Contact each company you are interested in working with and try to set up introductions at the meeting. Usually, everyone is very busy, but the exhibit hall is a great place to meet up. Larger companies will have medical affairs team members on site, possibly in a separate, smaller booth. Smaller companies may not even have exhibit space, but they may have MSLs assigned to attend the meeting. This method will allow you to get your name in with multiple companies, increasing the likelihood that some leads will be rewarding. Bring several copies of the introduction letter and site information you created, some in print and some on inexpensive memory sticks. As you peruse the exhibits, visit representatives from other companies and ask if you can drop off your materials for medical affairs. Follow-up with each contact by email and invite them for a site visit. Many MSLs like to travel to meet with physicians locally. Take the opportunity to get to know them, discuss the science behind their product and show them your site. This type of networking can help jump-start a new site's recognition process, making it increasingly likely it will get selected for a study. The steps leading up to beginning a study are demonstrated in Fig. 4.1. The timeline for these events is highly variable and can range from weeks to

months, depending on the motivation and resources of the sponsor and the ability of the proposed site to turn documents around after review. We have seen trials begin weeks after the receipt of the initial feasibility questionnaire, but a good middle ground is 3–4 months from the time the site turns in the questionnaire until the trial begins. Early phase trials may take longer. One aspect that induces variability is whether the sponsor has planned an investigator meeting for the trial. In this case, representatives from each accepted site travel to a central location to be trained in trial procedures, safety and recruitment. Other sponsors may conduct web-based training or conduct on-site training. Another aspect that may affect the timeline is the readiness of the site for the particular study it is being evaluated for. Often times, certain pieces of equipment or staff must be put in place before the SQS/visit is conducted.

Inset 4.4

Devices may be used for imaging or diagnosis. In this study of a Diagnostic Device, a prospective multicenter trial was conducted comparing clinical dermatologist diagnostic accuracy, skin pathology, and an imaging apparatus.

This is a prospective multicenter blinded study of 1,383 patients with 1,831 pigmented lesions. The device was compared to clinicians in evaluating pigmented lesions. Thirty-nine independent dermatologists were given a reader study of 50 randomly lesions (25 were melanomas) and compared to the results for a device. The device's sensitivity was 98.4 % and specificity was 9.9 % vs. 78 % and 3.7 %, respectively, for clinicians.

The performance of MelaFind: a prospective multicenter study. Monheit G, Cognetta AB, Ferris L, Rabinovitz H, Gross K, Martini M, Grichnik JM, Mihm M, Prieto VG, Googe P, King R, Toledano A, Kabelev N, Wojton M, Gutkowicz-Krusin D. Arch Dermatol. 2011;147(2):188–94.

Inset 4.5

Comparative effectiveness study of surgery to a device.

In this randomized, blinded, comparative trial, fifteen sequential subjects underwent minimally invasive fractional radiofrequency therapy. They were compared to six patients undergoing face lifts with similar baseline skin laxity scores. Skin laxity scores were compared. Face lift reduced skin laxity scores by 1.2 in a 4-point scoring system, and radiofrequency reduced laxity by 0.44 points.

Blinded, randomized, quantitative grading comparison of minimally invasive, fractional radiofrequency and surgical face-lift to treat skin laxity. Alexiades-Armenakas M, Rosenberg D, Renton B, Dover J, Arndt K. Arch Dermatol. 2010 Apr;146(4):396–405.

Another way to get involved in clinical research in addition to increasing your name-recognition is to submit a proposal for an investigator initiated study (IIS). According to a review by Surabhi Sharma, senior clinical research scientist at Novartis Pharmaceuticals, obtaining support for an IIS varies by company. Several purposes for an IIS may be considered. Examples include exploring a marketed product for new indications, new populations, additional dosage regimens, or in combination with other treatments. Safety and effectiveness data may be updated and a sense of scientific collaboration and exchange may be gained. An IIS proposal should be submitted with a curriculum vitae and an estimated budget for the trial. The proposal should include what the investigator would like from the company and may include test medication labeled and packaged for a blinded trial; placebo control; funding for included trial activities; assistance with protocol development and IRB submission as well as site monitoring, data management, safety monitoring and other services [22]. Proposals for IIS need not be lengthy. Often a one to two page synopsis of the proposed research is all that is needed for a potential sponsor's IIS review committee to determine if the research is a good fit. An example of an investigator-initiated trial in medical dermatology is an open-label trial involving ustekinumab for the treatment of moderate-to-severe psoriasis by Dr. Au et al. [23] in which the authors posed the question as to the effectiveness of an FDA approved medication for a treatment for which there was no standard management at the time. An example of an investigator-initiated device trial is a prospective clinical trial involving individuals with facial photodamage and actinic keratosis (AK). The authors sought to determine the 6-month safety, tolerance and efficacy of nonablative 1,927-nm fractional resurfacing for the treatment of facial actinic keratosis (AK) [24]. The rationale for this study using a device already approved for the treatment of AK was to determine if clearance rates could be extended beyond the time that had already been shown in prior research. In this example, the authors used a higher treatment density, which they speculated could have led to improved efficacy. Investigator initiated clinical trials can take on many forms and ultimately, are limited only by the imagination of the investigator, so long as the principles of GCP and ICH involving human subjects are strictly followed.

Inset 4.6

Key Protocol Items

- Methodology: is a step by step guide to each study visit. Elements include instructions for examining subjects, photographing skin lesions, taking biopsies, administering medication, and entering data in an electronic case report form. This section should be written clearly enough and in sufficient detail that any outside person could reproduce the study.
- Termination criteria: this covers end points, such as improvement in Psorasis Area and Severity Index (PASI) score by 10 %. This section often requires a statistician's help.
- Statistical plan: this shows the rationale for the size of the study and the breakdown of the subjects. One ethical principle for studies involving human subjects requires using as few subjects as necessary to answer a clinical question. Statisticians are a crucial member of the research team and are the best allies to determine study size and design.
- Informed consent: this is not just a document, but a process. The informed consent should be clear, easy to understand, and an integral part of all your subject evaluations. Unwillingness to give informed consent is a universal exclusion criterion.

Conducting clinical trials can be a challenging, yet rewarding experience that allows one to become intimately involved in the fascinating cooperation between medicine and industry. They are not for the faint of heart, but can be a wonderful addition to clinical practice for those who choose to accept the task.

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Chapter 5
Practical Tips

Ella Grach

Getting involved in a clinical trial requires a great deal of preparation. In order to secure the most equitable contract and most favorable budget, you have to do a thorough self-assessment of your resources, needs, and goals. You have to do a feasibility analysis to see if the contract and budget suit your particular situation. You need to understand the details of the contract and the protocol in order to negotiate from a position of strength. You need to understand your investigative site and staff capabilities and weaknesses honestly in order to negotiate from a position-based data and facts. The better you understand yourself and your site, the better you will be able to determine the feasibility of undertaking a protocol.

5.1 How Do You Get Established and Secure Your First Trial?

Unless you have documented clinical research experience, securing the first clinical trial could be difficult. There are a couple of ways to go about this process. Sponsors and CROs (Contract Research Organizations) use databases to identify Investigators and sites for their upcoming clinical trials. I would recommend registering with each CRO and with DrugDev.org. Another route, which is much easier, is to work with SMO, TMO (Trial Management Organization), or affiliate with a large dedicated research site in your region.

SMOs and TMOs will not only provide help with identifying clinical trials; but will help with managing some other very important aspects such as regulatory and IRB submissions, contract negotiation, marketing and advertising for your trials, and other important tasks. Some SMOs might even help you with subject recruitment or place an experienced coordinator in your office.

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A. Nasir (ed.), *Clinical Dermatology Trials 101: A Primer for Dermatologists*,
DOI 10.1007/978-3-319-09027-6_5

Fig. 5.1 The global investigative site landscape. *Source*: CenterWatch 2012 analysis of FDA-regulated investigators

There is a list of SMOs and dedicated research sites on the Center Watch website, www.centerwatch.com. Center Watch publishes a bi-monthly newsletter that in each issue provides a list of pharmaceutical companies and CROs actively seeking investigators for their upcoming trials.

You can work with a CRO or SMO and eventually should try to work directly with the sponsor whenever possible, especially if you become an established investigator; you'll get more visibility and a better contract. Because investigators have quadrupled to 30K, and NDAs have doubled, CROs are necessary. There are nearly 600 CROs out there, the biggest include Covance, Quintiles, Paraxel, Inventiv (Fig. 5.1).

In recent years, with changes in the healthcare arena, many physicians have considered getting involved in clinical research. The reasons for this have included alternative streams of revenue, fulfilling academic requirements, recognition among peers, specializing in a niche, getting published, and giving back to patients, the community, and the medical profession. Clinical trials are challenging, and require a great deal of training, organization, staff, and navigating a complex regulatory bureaucracy. Many investigators are first-time and one-time investigators. Annual surveys from the Tuft's Center for the Study of Drug Development indicate a consistently high turnover rate for Physician Investigators.

According to Tuft's data, in 2007; 26,000 Investigators registered with the FDA to conduct clinical trials; 85 % of the above registered physicians participated in only one trial (Fig. 5.2).

A lot of these physicians decided that research was not for them, or they did not have appropriate systems in place to support their research activities. While considering involvement in clinical research, several key factors should be taken into consideration:

Support staff: An essential staff member to have is a Clinical Research Coordinator (CRC). In my experience; nurses make the best coordinators. The CRC must handle a mix of clinical, administrative, business and marketing chores. Hiring a person with good personality is very important, because this person will become your

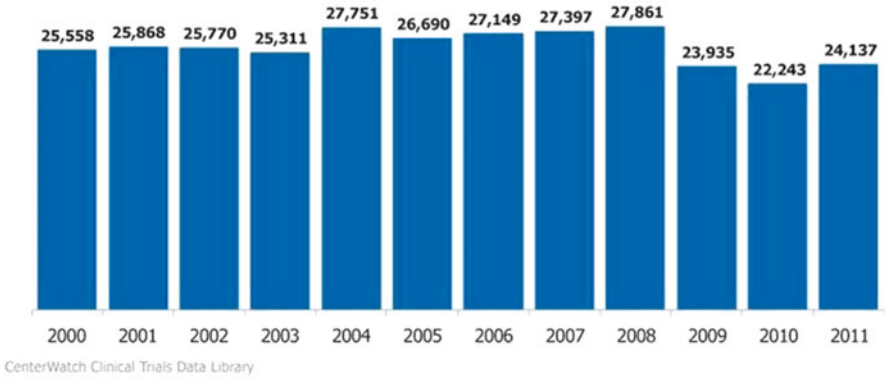

Fig. 5.2 Active unique investigators filing form 1572s worldwide. *Source*: FDA's Bioresearch Monitoring Information System File (BMIS)

liaison with Sponsors, Pharmaceutical and Biotech companies and CROs; and will be a leader for your patient recruitment and patient retention efforts. It would be a good idea to have your CRC be certified. Organizations like the ACRP and SOCRA grant certifications based on successful exams.

ACRP Certification, administered by the Academy of Clinical Research Professionals (the Academy), is the formal recognition of clinical research professionals who have met eligibility requirements and demonstrated proficiency of specific knowledge and job-related skills by passing a standardized exam www.acrpnet.org.

Space: The space issue can be overlooked by a novice Investigator; some clinical trials will require that patients to stay at the Investigator's site for more than a few hours. In addition to having regular practice exam rooms, you will need to provide an additional lounge or area so that the patient's who are staying for a longer length of time will be comfortable and be able to have access to television, internet access, snacks, etc.

The FDA regulation requires storing investigational drugs in a secure space. In addition, the drug storage area should be temperature and preferably, humidity controlled. Investigational "scheduled" drugs must be stored in a double-locked cabinet or a locked cabinet that is in a secured locked room.

Make sure to plan for study coordinator space, sponsor monitor work space, and study records archive room. Please note that FDA regulation requires you to store study records for at least two (2) years after study closure and in some cases for a much longer time. As you grow your operation and take on more studies, you may consider an off-site medical archiving facility.

Equipment: Some clinical trials might require equipment that is not customary for your practice. You will need to have a centrifuge, locked refrigerator, and either a −20 °F or −80 °F freezer (or both) which all must be monitored daily. For your convenience I am including a sample of a temperature monitor log for your review. If you do not already have it in your practice, a defibrillator and medical emergency kit is a must.

Patient database: Historically the majority of clinical trials conducted in the United States do not enroll study subjects within the sponsor-anticipated enrollment period. I feel that one of the most important tasks before starting a trial is a careful evaluation of protocol-required patient population and making sure that you have a sufficient amount of these subjects within your database. At our site, we call this a protocol feasibility process. We not only assess the protocol-required subject population under diagnosis, but also review our electronic medical records against the study inclusion and exclusion criteria. In addition, we take into consideration the study duration, number of visits required, and duration of each visit. Consider your patient's lifestyle, work situation, and age; they simply might not be willing to do the study because of time constrains.

Ask yourself a question: Will my patients benefit from participating in this trial? If the answer is yes, and you feel that you might be somehow limited with your patient database, consider reaching out to your colleagues in the medical community or advertising for the study subject. As we already mentioned above, all advertisement recruitment materials must be IRB approved. When considering approaching your colleagues for study subjects, please remember that incentive payments to healthcare professionals by Investigators for referral of study participants are known as referral fees. However, bear in mind that referral fees are not acceptable and may compromise the integrity of the research. In the (AMA) American Medical Association Code of Medical Ethics; Section 6.03 it is stated as follows: "Offering or accepting payment for referring patients to research studies (finder's fees) are also unethical."

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Some SMOs might even help you with subject recruitment or place an experienced coordinator in your office.

There is a list of SMOs and dedicated research sites on the Center Watch website, www.centerwatch.com (Fig. 5.3).

5.2 Investigator-Initiated Trials

Some sponsors will reserve funds for small investigator-initiated studies, especially if they want to create good will at the site. Usually, these are conducted at large academic medical centers, with funding through grants, which are written by the investigators.

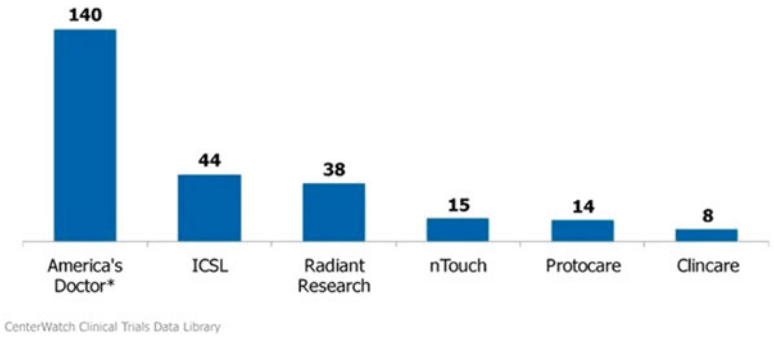

Fig. 5.3 Largest site management organizations in 2000 (number of sites in network). *Evolved into CRO service provider essential CRO; acquired by inVentiv Health, February 2010. *Source*: CenterWatch

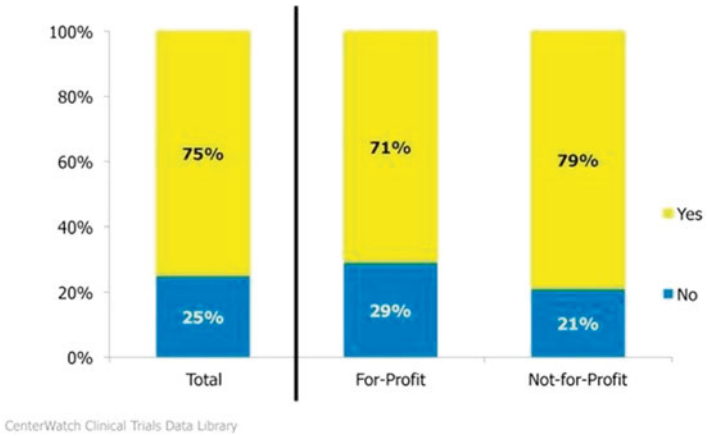

Fig. 5.4 Certification. Statistically significant at 95 %: none. *Source*: CenterWatch Clinical Research Coordinator Survey, 2012

5.3 Training and Certification

SoCRA developed the Certified Clinical Research Professional Certification program to evaluate a CRPs knowledge, understanding, and application of the conduct of clinical investigations involving humans in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice (E6) (ICH/GCP), the United States Code of Federal Regulations (CFR), and the ethical principles that guide clinical research consistent with the principles of the Nuremberg Code, the Belmont Report, and the Declaration of Helsinki www.socra.org (Fig. 5.4).

5.4 SOPs

In clinical research, SOPs help define the Practice's Research Department or Research Site standard practices and internal processes conducted to assure execution of research studies in accordance with Federal and State Regulations.

SOPs should guide research staff through a particular procedure and provide uniformity in the daily functions of the research department. The SOP should be written in a generic format to allow for easy implementation across a broad set of various aspects of multispecialty trials, but yet should specifically define procedures that can be followed without deviation.

The SOP should include the objective of the SOP, definition of key terms and acronyms. SOP must reference applicable guidances and regulations within the SOP, such as ICH E6 Good Clinical Practice and 21 CFR 50. The SOP should include the signature of the Research Administrator or Director with the date of approval.

SOPs should be reviewed at regular intervals (preferably annually) to reassess applicability of the policy.

Research staff should be educated and trained on SOPs. I suggest documenting the date when research staff have been appropriately trained and agree to comply with SOPs. Your staff should be monitored to ensure compliance and receive refresher training at regular intervals.

The following topics should be covered in your SOPs:

1. SOP: Preparation, Issue, and Revisions
2. Organizational Chart
3. Master Study File and Record Retention
4. Site QA and QC
5. Subject Screening Procedures
6. Informed Consent
7. Study Initiation Visit
8. Subject Study Visits
9. Study Data Collection and Review
10. Drug Storage, Inventory and Accountability
11. Lab specimens Collection, Preparation and Shipment
12. AE/SAE Documentation and Reporting
13. Communication with and Reporting to IRB (protocol departures, AE/SAE reporting)
14. FDA Audit Preparation
15. Study Close-out Visits
16. Protection of Subject PHI and Site HIPAA Compliance
17. Medical Emergency Procedures
18. Staff Training

5.4.1 Source Document

Source document for a clinical trial might include, but is not limited to, the following: subject's medical record, any protocol worksheets created for the study, and properly executed ICF. In addition, it may include other documents such as:

- Subject Study diaries and questionnaires
- EKG records
- Laboratory reports
- Letters and Memos
- Original radiological films or Reports
- Pathology slides
- Tissue blocks
- Drug dispensing log
- Drug administration data (Medicine Administration Record—MAR)
- Adverse events Serious Adverse Event log

5.4.2 Emergency Action Plan

During Katrina in 2005, there were 750 trials taking place at the Ochsner Clinic in New Orleans. Subjects had diseases from cancer to diabetes, from AIDS to COPD. All communication, including cell phones, and internet were disrupted. Only text messaging still worked. There was a huge loss to studies. Costs included patient contact information, data, and specimens. Furthermore, investigators left, 17 NIH funded labs at $5.7 M/year left LSU for institutions in other states. In 2012, Hurricane Sandy flooded New York City. Redundant generators providing power for NYU were unfortunately kept in the basement, where they flooded and malfunctioned. Patients had to be evacuated through stairwells because the elevators were not working. Some research records were destroyed.

Disasters happen, and can cripple research in any location. Backups can help protect your data. It's a good idea to get as much contact information on subjects as you can (cell phone, email, and next of kin outside the area, if possible), store it in a secure place, and back it up off-site. Use radio communication with subjects after a disaster. You can call a news station and have them broadcast on the radio that your subjects are safe until authorities can arrive. Have contact information for local news and radio stations handy. Have remote storage and backup of all your data.

5.5 Feasibility

Feasibility is assessed at several levels. It is defined as the process of determining whether a trial can be conducted at your location given the parameters provided to you by your sponsor. Feasibility is very important to your sponsor, because nearly a 1/3 of the delay of clinical trials is due to subject enrollment. About 1/5 of investigative sites don't enroll any subjects and about 1/3 of sites enroll only 5 % of total subjects. For sponsors, only 1/3 of the sites reliably enroll volunteers. You want to make sure you are in that 1/3 category. If you are, you will be in good company, and you will be invited back for future studies.

Feasibility at the program level is defined as an entire program, for example inflammatory skin disease, or cutaneous oncology. By definition, the scope of program level feasibility is broad. You have to decide if such a program has a reasonable chance of success in your area. For example, you may have a clinic in a small college town. The majority of your patients may be students, and the other faculty and residents of the town may be small in number but relatively young. A cutaneous oncology program focusing on skin cancers of the elderly may not be suitable for your research enterprise.

Feasibility at the study level has to do with your assessment of whether a study is doable. You want to analyze it from a clinical standpoint to see whether it is reasonable, but you also want to see if the regulatory, technical, and operational hurdles of the study are easily surmounted. Ask yourself if the protocol has any requirements which depart significantly from what you consider to be an acceptable study and clinical practices. Ask yourself if the regulatory burdens of the study allow it to be approved in a reasonable time frame, or if you will require time and resources to evaluate the study and get the approval of others in your research group, or other regulatory or administrative body. The study should require readily accessible technical tools, or supply them. Make sure there are no operational challenges to your efforts. For example, if your research center is in a community with several academic institutions or research centers, make sure that nearby sites are not being considered or haven't been selected. This could hurt the sponsor and would hurt you, because nearby sites would be competing for volunteers from the same recruitment pool.

5.6 Protocol Feasibility

You will likely have to sign a confidentiality letter before you can look at a protocol. When you are reviewing a protocol, it is important for you to determine if it is feasible for your site. It is preferable to opt out of a study which is not suitable for you than to accept one and be unable to complete it because of foreseeable obstacles. Your ability to conduct and complete studies will build your reputation and attract more studies and sponsors. If you are regularly unable to fulfill study obligations, you may dim your prospects as an investigator.

First make sure you don't have any competing trials. You will duplicate your efforts and dilute your enrollment. Ask yourself if you've done similar studies, and whether they were successful. If so, this is a good sign that the current trial is suitable for your site. The enrollment criteria should be clear and should be suitable for your patient population. Sometimes inclusion criteria are unclear. For example, if a protocol for psoriasis requires patients to enroll who are not taking steroid medication, without specifying how much steroid medication, for how long, and by what route (oral, topical, inhaled), you may inadvertently exclude or enroll the wrong subjects. Think about other factors which may hinder subject enrollment. For example, are subjects too young or too old? Does the study last too long (years?)? Are study visits too frequent, and would they interfere with the subjects' daily lives? Is the dosing of the medication too frequent, or impractical (for example, after applying topical study drug, subjects must wait an hour before washing or wearing makeup)? The washout period allows subjects who are taking prohibited medications to discontinue the medications for a set period before being eligible for a trial. For example, subjects in a trial for atopic dermatitis may be allowed to start the trial after avoiding all topical steroids or topical immunomodulators for 4 weeks. Are there too many prohibitions on concomitant medications? Is the washout period too long, or too strict? Are there any procedures which cause undue discomfort to patients?

When reading the protocol, it's important to ask yourself if criteria are vague, or unclear, or too strict. You can jot notes in the margin and bring up your questions during a site qualification visit or during the investigators meeting. Sponsors welcome Site/Investigator feedback. They want you to succeed and they want the study to succeed. It suggests an attentive and interested investigator. Often, the protocol will be amended based on Investigators feedback. The appointment times for visits should be suitable for your schedule and subjects' schedules. A study with rigid visit windows over the holiday season may have limited enrollment or a high drop-out rate. A year-long study which requires that the same investigator evaluate a subject at each visit without provisions for substitute sub-investigators or co-investigators may not be feasible, or require a special subject retention plan. A study medication which requires occlusion with adhesive tape may not be suitable for subjects in a hot humid locale in the summer. If you find an obstacle in the study, try to think of suggestions to overcome it. A study drug for actinic keratosis which excludes patients with a history of skin cancer of any type could potentially be modified to include patients with a nonmelanoma skin cancer which has been successfully treated. You also need to determine if the sponsor has adequate resources and personnel to support you in the trial. If the trial requires specimens be shipped to a central laboratory, clearly marked shipping containers should be made available. If a protocol requires biopsy specimens to be snap frozen in liquid nitrogen and shipped on dry ice to a central laboratory future genetic analysis, be sure you get details. Look in the protocol for step-by-step instructions on obtaining and preparing the specimen. Check that you are supplied with all the necessary materials and reagents, including biopsy kits, sutures if necessary, specimen vials which are stable to snap freezing, liquid nitrogen and personal protective equipment for its handling, dry ice, insulated mail

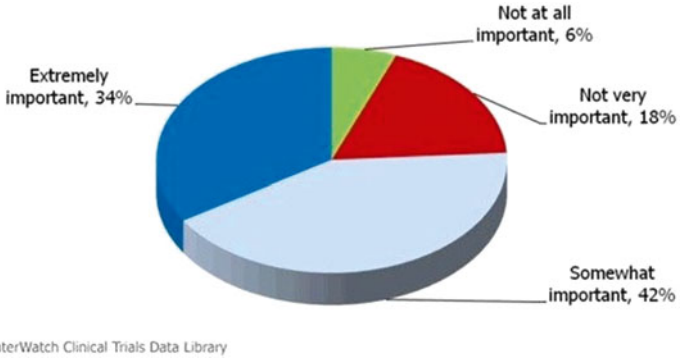

Fig. 5.5 How important is protocol design to your decision to participate in a clinical trial? *Source*: CenterWatch Survey of 1,329 investigative sites, 2010

containers, added cost for transporting specimens, and clearances for shipping human tissue. It's not good to find out midway in the study that a particular supply item is an out-of-pocket cost to you, or that your shipping container is not labeled or suitable for human specimens (Fig. 5.5).

Determine if you need specialized equipment. If this is something that needs to be purchased, is it in the budget? If this is something that you can lease or borrow from colleagues or a third party, will you be reimbursed for your costs? Ask where the study is conducted. Determine if the care is provided exclusively in your office, or your study site, or the hospital. Find out if you can see subjects in all locations, or if only certain sites can be used for part or all of the study. This is particularly important if you are working with co-investigators at multiple locations. Your sponsor, or the trial may insist that only one physical site be permitted for subject assessments. You may still be interested in such a trial, but you may have to be sure that travel times to the site and patient evaluation windows do not conflict. Ask if any special personnel are required to conduct the study. For example, you may be doing a trial on a biologic agent such as a tumor necrosis factor inhibitor, which is known to have potential cardiac toxicity, and may be required to do an electrocardiogram which is read by a board-certified cardiologist. Or, you may be required to administer a study drug intravenously. This will require trained and qualified staff. Ask if you will need to see subjects outside of standard clinic hours. For example, in phase I trials, some pharmacokinetic measurements need to be done over a 24-h time frame. Be sure you have the capability to deal with this exigency. Determine if, in your clinical opinion, adverse events, particularly severe adverse events are to be expected, or likely. This will add to your cost and time. You will need to budget accordingly. Alternatively, you may not be able to participate in a study of a medication fraught with burdensome side effects.

You also want to vet your sponsor or SMO/CRO. You want to research your sponsor's track record, particularly in dermatology studies. You want to make sure they are adequately funded and have qualified and responsive personnel. You want to see that their protocol is well-thought out and well-written. If you find too many

gaps or have to make too many suggestions and amendments just to get the protocol off the ground, of if your comments are brushed aside or disregarded, you may need to reconsider your collaboration with this Sponsor. You also want to gauge the sponsor's long-term health. If you are audited by the FDA 2 years or 10 years after the study is completed, will the sponsor still be around?

5.7 Study Feasibility Checklist

Administrative support: from your practice manager, or your hospital or institution. If your institution doesn't support you, you'll have a difficult task succeeding in the study.

Subject recruitment/retention: How will you recruit subjects? Will you be able to get enough? Are the enrollment criteria reasonable or too restrictive? Does the sponsor help with recruitment? How sick is the subject population (greater risk of AE, SAE). Are there known risks for a similar class of drugs? How interesting is the study to you, or to your subjects (Botox)? Will you be able to retain your subjects? What compensation do they get? Is it fair or coercive? What about medication at the end of the trial?

- You'll need to screen many more subjects than you think. Typically 1 out of 16 potential subjects enrolls in a study, a rate of about 1 patient per month. The math is as follows: halve potential patients (lack of interest), halve again (childbearing), halve again (won't or can't consent), halve again (meet inclusion/exclusion criteria).
- Keep track of your recruiting data and success rate. It will help you in future studies.
- Knowing your screening-to-enrollment ratio helps you budget better. You need to know how many subjects you will have to screen in order to enroll one volunteer. You need to be aware how much time this will take. When you look at the inclusion and exclusion criteria, you have to determine if they are straightforward or time consuming, and budget accordingly.
- If you share your misgivings about a study, the sponsor may relax the inclusion/exclusion criteria to help you meet your goal.
- Attend investigators meeting (usually held before study initiation) where protocol is reviewed, and investigators have a chance to express their concerns and offer suggestions, and learn about the disease process being studied.
- Designate a staff member with good interpersonal skill and good telephone manners to be your Subject Recruiter.

Compliance: is it too difficult, too uncomfortable, too tightly scheduled leading to high dropout rates? Will subjects have to miss school, work, vacation? Is dosing inconvenient, difficult, painful? Is there flexibility in the time schedule, or is it very rigid?

Personnel: do you have enough and do they have the right skills? If not, who will provide the training? How much time will training require, and will it take them away

from other commitments? Do they understand their roles and responsibilities? Do they understand the ethics of clinical research? Do they understand confidentiality, HIPAA, FAA (Federal Aviation Administration) shipping regulations, OSHA regulations? Do they have the appropriate vaccinations and personal protective equipment?

- PI: overall responsibility for the protocol, follows GCPs, federal and local regulations, ensuring proper subject consenting for the trial, properly delegate study-related task to well-trained and qualified site personnel, promptly report AEs and SAEs, serving as the patient care liaison between the sponsor and the IRB, makes medical assessments, provides guidance and oversees all members of the research team.
- Study coordinator:
  - Helps determine study feasibility for the site
  - Assist the Investigator with performing all study-related tasks
  - Unless your site has a designated regulatory associate, your coordinator might be involved with handling and tracking study documents:

    FDA 1572
    CVs for all those listed in FDA 1572 and Financial Disclosures
    IRB submission packet (protocol, consent, Investigator brochure)
    Licenses (must be annually updated for each member and lab)
    Maintaining the Regulatory binder
    IRB and sponsor correspondence
    Study guides and worksheets

  - Manages logistics

    Schedules monitor visits, patient visits
    Tracks patients study activities
    Maintains study supplies
    Assisting PI in subject selection and screening activities according to protocol inclusion/exclusion criteria
    Takes part in subject consenting process
    Performs non-MD study-related tasks

  - Coordinates monitor activities

    Prepares case report forms (CRFs)
    Makes sure all source docs are available
    Assisting the sponsor monitor during their Site Visits
    Works as a liaison between the lab, pharmacy, radiology, administration, IRB, dietary, housekeeping, etc.

Regulatory: can you meet IRB and consent requirements?
- IRB packet contains the protocol, amendments, informed consent, and the Investigator Brochure.
- Approval letter from IRB should include:

Name, address, and chair of IRB.
Name of contact person at IRB.
Name of the protocol and protocol identification number.
PI name and contact number.
Date of IRB approval.
Documents reviewed (protocol version number, amendments, etc.).
IRB decision (approval, not, any modifications).
IRB certification and list of members.
Signature of IRB chair.
Expiration date of approval.
Where the study may be conducted.

5.8 Regulations

5.8.1 Understanding the Regulations

In October of 2009 US Department of health and Human Services Food and Drug Administration issued a Guidance for Industry on Investigator Responsibilities—Protecting The Rights, Safety, and Welfare of Study Subjects.

The following excerpts from the guidance provide an overview of the responsibilities of a person (an Investigator as defined in 21 CFR 312(b)) who conduct a clinical investigation of a drug, biological product, or a medical device.

5.8.1.1 Overview of Investigator Responsibilities

In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible for:

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations
- Protecting the rights, safety, and welfare of subjects under the investigator's care
- Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

Investigators who conduct clinical investigations of drugs, including biological products, under 21 CFR Part 312, commit themselves to personally conduct or supervise the investigation. Investigators who conduct clinical investigations of medical devices, under 21 CFR Part 812, commit themselves to supervise all testing of the device involving human subjects. It is common practice for investigators to delegate certain study-related

tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

What Is Appropriate Delegation of Study-Related Tasks?

The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task. Appropriate delegation is primarily an issue for tasks considered to be clinical or medical in nature, such as evaluating study subjects to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing medical care to subjects during the course of the study. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. Licensing requirements may vary by jurisdiction (e.g., states, countries). Investigators should take such qualifications/licensing requirements into account when considering delegation of specific tasks. In all cases, a qualified physician (or dentist) should be responsible for all trial-related medical (or dental) decisions and care.

During inspections of investigation sites, FDA has identified instances in which study tasks have been delegated to individuals lacking appropriate qualifications. Examples of tasks that have been inappropriately delegated include:

- Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria
- Physical examinations
- Evaluation of adverse events
- Assessments of primary study endpoints
- Obtaining informed consent

The investigator is responsible for conducting studies in accordance with the protocol (see 21 CFR 312.60, Form FDA-1572, 21 CFR 812.43 and 812.100). In some cases a protocol may specify the qualifications of the individuals who are to perform certain protocol-required tasks (e.g., physician, registered nurse), in which case the protocol must be followed even if state law permits individuals with different qualifications to perform the task (see 21 CFR 312.23(a)(6) and 312.40(a)(1)). For example, if the state in which the study site is located permits a nurse practitioner or physician's assistant to perform physical examinations under the supervision of a physician, but the protocol specifies that physical examinations must be done by a physician; a physician must perform such exams.

The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks and identify the training that individuals have received that qualifies them to perform delegated tasks.

What Is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?

For each study site, there should be a distinct individual identified as an investigator who has supervisory responsibility for the site. Where there is a subinvestigator at a site, that individual should report directly to the investigator for the site (i.e., the investigator should have clear responsibility for evaluating the subinvestigator's performance and the authority to terminate the subinvestigator's involvement with the study) and the subinvestigator should not be delegated the primary supervisory responsibility for the site.

The investigator should have sufficient time to properly conduct and supervise the clinical trial. The level of supervision should be appropriate to the staff, the nature of the trial, and the subject population. In FDA's experience, the following factors may affect the ability of an investigator to provide adequate supervision of the conduct of an ongoing clinical trial at the investigator's site:

- Inexperienced study staff
- Demanding workload for study staff
- Complex clinical trials (e.g., many observations, large amounts of data collected)
- Large number of subjects enrolled at a site
- A subject population that is seriously ill
- Conducting multiple studies concurrently
- Conducting a study from a remote (e.g., off-site) location
- Conducting a study at multiple sites under the oversight of a single investigator, particularly where those sites are not in close proximity

The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified and experienced.

A plan might include the following elements, to the extent they apply to a particular trial: Routine meetings with staff to review trial progress, adverse events, and update staff on any changes to the protocol or other procedures

- Routine meetings with the sponsor's monitors
- A procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study
- A procedure for documenting or reviewing the performance of delegated tasks in a satisfactory and timely manner (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)
- A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that study subjects understand the nature of their participation and the risks
- A procedure for ensuring that source data are accurate, contemporaneous, and original
- A procedure for ensuring that information in source documents is accurately captured on the CRFs

- A procedure for dealing with data queries and discrepancies identified by the study monitor
- Procedures for ensuring study staff comply with the protocol and adverse event assessment and reporting requirements
- A procedure for addressing medical and ethical issues that arise during the course of the study in a timely manner

The investigator is responsible for supervising the study tasks performed by this staff, even though they are not in his/her direct employment during the conduct of the study. This responsibility exists regardless of the qualifications and experience of staff members. Links to specific guidelines can be found on the FDA website; www.fda.org.

5.9 Institutional Review Board

Once your study site has been selected, the submission process to the IRB can begin. Be sure you budget for this process, as it is time consuming, and expensive. IRBs can be institutional, local or central, and they need specific documents in order to review a study.

Investigators must obtain approval from the IRB prior to conducting the study. When conducting a clinical trial; the safety of human subjects is paramount. IRB is safeguarding protection of human subjects in clinical trials. As per FDA (21 CFR—56.102(g)) is " any board, committee or group formally designated by an institution to review, approve the initiation of and to conduct periodic review of biomedical research the protection of the rights and welfare of the human subjects."

There are two types of IRB: "local"—(local IRB is usually attached or connected to the institution) and "independent" (independent IRB—which I call commercial, or central; these IRBs are not affiliated with a local institution and can be utilized by any institution or by anyone who does not have an IRB. Sponsors prefer to use independent IRBs especially for multicenter studies because independent IRB's turnaround time is much quicker than institutional IRB's. FDA requires that IRB's membership must include at least five (5) members (some IRB's include alternate members as well); with varied backgrounds to include scientific and nonscientific professions, diversity, ethnicity, and gender.

5.9.1 IRB Review

In order to review and approve research study; IRB will review:

- *Investigator qualifications*: Investigator must submit to IRB a current signed CV that includes education, training, and experience to include any licensing and/or board certification.

- *FDA Form 1572*: Statement of Investigator Form—This form is required for all FDA-regulated studies under Investigational New Drug Application (IND). FDA Form 1572 is not required for device studies.
- *The study protocol*: Including the following elements; the title and sponsor of the study, the purpose of the study, background of studying investigational compound/or device, results from previous related research, primary and secondary end points of proposed research, study design; including discussion of research methods, study subject population, subject inclusion/exclusion criteria, description and schedule of procedure and events, provision for managing adverse/serious adverse events.
- *Supporting documents (investigational brochure and/or package insert)*
- *The proposed informed consent form (containing all required elements)* and providing information for protecting of subjects privacy, compensation for research-related injuries. Payment to subjects (stipend) for their trial participation.
- *Proposed advertisement*: This would include anything that would be directed towards potential research subjects and designed to recruit them for participation.
- *Any other forms*: That may be used in pre-screening subjects (i.e., pre-screening forms, instructions to subjects).

Throughout the conduct of the study the Investigator must report any protocol changes or protocol amendments to the IRB. All changes or amendments must be approved by IRB prior to implementation and may require changes to informed consent forms. Investigators must promptly report to IRB "reportable" adverse events and serious adverse events. In addition, any protocol violations and deviations must be reported to IRB.

Publicity of a general nature does not require IRB review. For example, if you have a research site that does a number of dermatology clinical trials, you may advertise your site as long as you do not use that publicity to recruit subjects for a particular study. You are also permitted to make a list of the clinical trials you conduct on your website, and may include details such as the title of the trials, their purpose, a summary of the protocol and its eligibility criteria, the location of the study site(s), and contact information. You are not permitted to use incentives to recruit subjects, including finder's fees, direct recruitment incentives, or bonuses of any type to enroll study subjects. You also may not cold call subjects, unless they are in your study database and have already agreed to be in a registry and contacted about future trials. General advertisements are also not allowed, because they can quickly be out of date. Each advertisement must be made for specific study.

The review process can be Exempt, Expedited, or Full. Exempt studies typically fall into six categories under the FDA's 45 CFR 46.101(b) or 21 CFR 56.104. These include studies which are on food taste and quality, public service programs, analyzing already gathered data without subject identifiers, educational tests and standards.

Expedited reviews fall into several categories, all of which require minimal or no risk to subjects. These include provisions for drugs (21 CFR Part 312) and devices (21 CFR part 812) for which applications are not required. There is a category for the collection of blood samples by finger stick, heel stick, ear stick, or venipuncture, a category for the

prospective collection of biological specimens by noninvasive methods (such as hair and nail clippings in a nondisfiguring manner, secretions such as sweat, and mucosal and skin cells collected by buccal scraping, mouth washings, or skin swab). In October 2010, the OHRP agreed with the FDA that vaginal swabs not beyond the cervical os, and rectal swabs not beyond the rectum are also noninvasive. There is another category for noninvasive data collection including weighing, height measurements, skin lesion measurements, ultrasound, diagnostic infrared imaging, and dermoscopy. There is a category for research on materials collected for non-research purposes. For example, blood that was previously collected and analyzed for a clinical result. This is detailed in 45 CFR 46.101(b)(4). There is a category for collection of voice, video or images collected for research purposes. The privacy of subjects obviously has to be protected. However, studies in this category do not merit expedited review if accidental identification of the subject might place them at risk (for example, civil liability, criminal liability, financial damage, employability, insurability, reputation, or any stigmatization). There is a category on individual or group behavior. For example, studies on itch perception, cultural beliefs surrounding tattoos, and motivation to comply with a topical medication. There is a category for continuation of a study which has been closed. And there is a catch-all expedited category in which the IRB determines that the only category met is minimal or no risk to study subjects.

As part of the application, each study requires the identification of a principal investigator (PI). The PI takes full responsibility for the conduct of the entire study. Examples of study PIs include curators, instructors, librarians, non-tenure-track research faculty, tenure track faculty, senior investigators, and clinicians. Most dermatology studies require that the PI be board certified in dermatology. You and anyone you have authorized to participate in the design or conduct study, such as your co-investigators and sub-investigators, need to be on FDA Form 1527 and on your IRB application. You also need to name contact persons in recruitment forms and informed consent documents. If you have an electronic IRB, you may need to register electronically. You also need to complete and document human subject research training that is current in the last three years. Many IRBs and sponsors withhold approval or consideration of a study if this training is not up-to-date.

You may have additional reviews if the study requires it. For example, if you require the release of clinical specimens from the clinical laboratory or pathology department, you may require a separate review and application. If your study requires inpatient care, you may have a special hospital committee, or nursing committee review the study prior to approval. The skin has been shown to be a powerful reservoir of stem cells. You may have a separate review process for induced pluripotent stem cell research.

5.10 Study Flow

There is a flow to every study, and it helps in your organization process to understand it. All studies typically have four study flow phases for investigative sites. There is a pre-study phase (selection phase), during which you and the sponsor get a sense of each other's abilities and compatibilities. There is a study phase during which the necessary training and protocol procedures are performed (SIV—Site

Initiation phase). The study conduct phase is a main and possible longest in duration phase, accounting for actual study enrollment and treatment/subject follow-up portion. There is a post-study phase during which you and the sponsor may be in contact for follow-up or in case of an audit.

5.11 Study Tracking

There are commercial study software packages, i.e., Study Manager, which help you keep track of study procedures and important dates and windows. You need to have a screening and Enrollment Log. It is very important to document all reasons for subjects screen failing the study and report them back to Sponsor. If Sponsor consistently sees the same reasons across the board, they might consider amending certain protocol I/E criteria.

Patient Outcome Log helps track outcomes and makes a final report to the sponsor or IRB easier. Include date, gender, age, and underlying disease. It's better to record this information as you get it rather than waiting until the end of the study. Once the study is complete, you can send a quick summary to the IRB.

5.12 Billing

When you are running an active practice and conducting clinical trials, how do you keep study and non-study charges separate? You have to review the consent, protocol, and contract for any conflicts in what is paid for by the sponsor. The FDA Common Rule requires patients to fully understand any additional costs for participating in the study. Unexpected study charges related to untoward reaction from study drug should be billed to the site and not the patient. The site can then ask for reimbursement from the sponsor.

5.13 Worksheets

This is a flow sheet or spreadsheet which helps you capture data: signs and symptoms, physical exam results, medications, laboratory data, etc. You can make your own or sometimes it can be provided by a Sponsor. Color coding can help you separate studies. Color coding can also help study visits stand out in paper charts.

5.14 Pre-study Visit or Site Qualification Visit

Sponsors and monitoring sites know how expensive it is to conduct clinical trials. They don't want to extend a contract to do research to your site without proper due diligence.

Depending upon your circumstances, a sponsor may wish to conduct an in-person, telephone or web-based interview with you to gauge your interests and experiences in participating in a clinical trial. Some studies require a so-called pre-study evaluation. Under some circumstances, the requirement may be waived. For example, the sponsor may have recent (in the last 18 months) experience with the investigator or site on a similar or related trial.

The pre-study visit will have several objectives. The interviewer will want to get a sense of your site, your facilities, the training and certification of your staff, whether or not you have a suitable database of potential study subjects, and your level of interest or enthusiasm in the study. If you don't show your motivation, or if you are involved in competing studies, your site may not be selected.

Take these sessions seriously. Allot anywhere from 2 to 4 h of you and your staff's time to answer the start-up monitor questions. Also use the time to assess the suitability of the sponsor for your site. Once your visit is complete, you will likely get feedback in the form of a letter regarding your acceptance to the study. If you are not accepted, learn from your experience. Ask yourself, and the monitor, what you could have done differently and can do in the future to secure studies.

Your monitor may ask you to fill out a questionnaire and give a copy of your current CV. You may be asked innocuous sounding questions designed to gauge your knowledge of the study or of guidelines and regulations such as GCP, FDA regulations, and ICH guidelines.

Monitors are constantly asking themselves if your site will perform well, or be a "dud." Will you be efficient and strictly adhere to protocols, or will you be sloppy and require constant coaching, badgering, and multiple time consuming interventions to keep you on track? Will you successfully recruit subjects, or did you promise more than you could deliver in accepting a study? Will you complete the study, or will your site be closed early because of nonperformance? Monitors know that some investigators and sites consistently meet or exceed expectations. They have a track record of success and audit survival. If you are one of those investigators, you are in demand, and you will be approached. If you have no record of success, you will need to make your best presentation at the visit.

Monitors will be gathering information about you from your publications, attendance at conferences, feedback from pharmaceutical and device representatives, online lists of investigators, other monitors in the industry, and watchdog websites such as: http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/default.htm http://www.accessdata.fda.gov/scripts/cder/cliil/ http://silk.nih.gov/public/cbz1bje.@www.orilist.html.

Monitors will also be getting a sense of your communication style, and the general atmosphere of your facility: whether it's relaxed and focused, or tensed and disorganized. You can also use the opportunity to get a sense of the monitor's style and the sponsor's qualifications. You don't want to work with a monitor who is brusque or uninformed. You don't want to work for a sponsor where there is high turnover or little support for investigators, especially during audits. And you don't want to work with a sponsor on shaky financial footing. You don't want the sponsor to go bankrupt while you are in the middle of a trial.

5.15 Initiation Visit

The initiation visit is scheduled after your acceptance/selection for the study and sometimes could be months after the site qualification visit. Usually, at this time, the sponsor will review items you have long since forgotten (protocol, Investigational drug background information, inc/exc criteria, study activities, procedures, any changes to the protocol based on the investigator's meeting).

During your initiation visit you will probably spend a great deal of time training or reviewing the study protocol design and answering questions from the site personnel. You will also want the Principal Investigator (PI) to be available for specific parts of your presentation. Specifically, you will need to discuss the Investigator's Responsibilities as related to the regulations to ensure there is agreement and understanding. The investigator may choose to delegate some of his/her responsibilities but ultimately, they will be responsible for all actions and conduct of the study. Specific study-related activities can only be delegated to those who possess adequate training and experience.

You'll want to hit the ground running. There is an urgency, because of cost, to get patients in and going. Drug companies operate on constrained time lines and may just drop you if you don't meet enrollment. The sponsor has a desire to beat its competition for being first in its class. A drug that is first in its class gets publicity, name recognition, and becomes the go-to standard. Early approval boosts sales, and maximizes the patent clock. You could also be dropped if your subjects are not evaluable (i.e., in a *T. pedis* study, you could have positive KOH stains at your site, but cultures could be negative). Enrollment is competitive and limited, and you want to make sure your site meets its targets. Your administrative costs are the same whether you enroll one or dozens of patients.

5.16 Study Subject Recruitment

The recruitment phase costs 27 % of the budget, the most expensive and difficult part of drug development ($2B/year). Recruitment has become more difficult because the FDA has tightened criteria for efficacy, and because multiple companies are looking at the same pool of potential volunteer subjects. Also, sites may need to screen 10–20 subjects to identify one viable candidate, and sponsors don't often compensate adequately for screening.

You have to decide if you have an adequate number and type of subjects who are suitable for the study. You can do this by carefully reading the inclusion and exclusion criteria for the study and matching to your existing subject base. It is good for you to start an enrollment log before your first study. This should have information such as the various studies you have participated in or plan to participate in, the phase of the trial, the number of subjects required for the study from your site, the number of subjects you screened, the number who were included in the study, the number who completed the study, and the number who dropped out, as well as

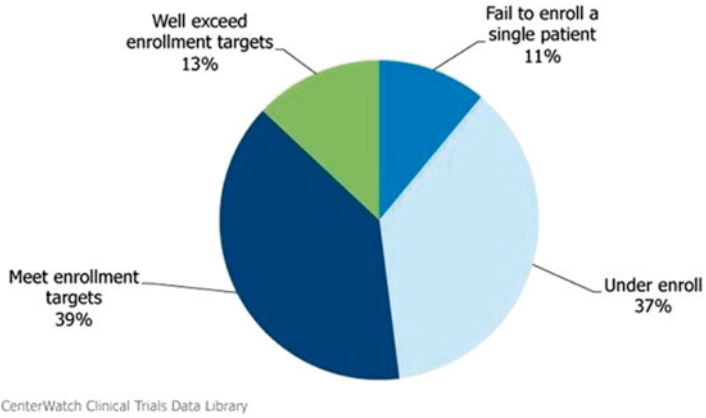

Fig. 5.6 Typical site enrollment performance. *Source*: Tufts CSDD, 2011 <csdd.tufts.edc>

their reason. You will be asked as part of the study to determine if you can enroll an adequate number of subjects. You will be given a time window in which to do so. You can estimate your probability of success by estimating the number of subjects with the disease state in question you could see in a month, and determine the ratio of your screen to failure. For example, if you see thirty patients with severe nodulocystic acne each week, and 120 such patients each month, and you think (or know from previous similar studies), that each month, 12 patients (10 %) would be eligible to screen, and that 6 (50 %) would likely participate in the study, you could recruit about 6 subjects per month. If the enrollment period were 3 months, you could enroll about 18 subjects in that time period. If the enrollment minimum for your study site were 10, you could easily meet your requirements. If enrollment were competitive with other sites, you might be able to enroll even more subjects. If, however, the enrollment minimum for your site was 50 subjects, you would not meet minimums. You could either bow out of the study, or ask the Sponsor about supporting you with advertisement funds (Fig. 5.6).

Your source of subjects depends on a number of factors. If you are a practicing dermatologist, and you are conducting dermatology clinical trials, you may simply seek volunteers from your practice. You can notify your patients on a case-by-case basis, by bringing up a study which you think would benefit your patient. For example, you may have a number of patients with verruca vulgaris, most of whom you manage easily in your office. You may have a handful with intractable periungual verrucae, myrmeciform verrucae of the soles, or stubborn verruca plantaris. You may have used multiple therapeutic modalities, all without success. If you are selected for a trial on a new therapy for intractable warts, you could bring it up to such patients as they come into your office. The advantage of this strategy is that the patient is already there to see you. The drawback to this strategy is that—unless your practice is overrun with patients presenting with common warts and sees a fair number with intractable warts on a daily basis—it may take too much time. If your enrollment window is long (on the order of months or a year), and the enrollment numbers are low, and the

competition with other sites for subjects is low, you can take your time, and will likely meet your enrollment minimums. If—as is more often the case: sponsors are pressed for funds, and time is money to them—enrollment windows are short, and you are competing with many sites for subjects, you may not be able to meet your minimums by a "wait and see" who walks in the door approach. You would be better served by having some way to reach your patients with stubborn warts. You could post a flyer in your waiting room, or post a notice in each examination room. The contents would have to be approved by the IRB or the sponsor, as it could be construed as an "advertisement." It could describe the study and allow potential subjects or their family members to see if they were eligible for the study.

If you have a way of analyzing your practice and reaching patients with certain diagnoses, you have a much more powerful tool to recruit study volunteers. A secure HIPAA-compliant database of potential subjects, stratified by diagnosis, can be an efficient means of determining if you have potential subjects for a study. Large institutions and academic centers mostly have these databases. Dedicated clinical research institutes also utilize these.

Even if you have a small practice, you may have a database searchable by ICD diagnosis code as a component of your electronic medical record or billing and scheduling software. Using appropriate search criteria, you may be able to contact subjects for potential eligibility in upcoming or ongoing clinical trials. As you become more familiar with your practice and the trials you conduct, you may be able to use non-obvious search criteria for study subjects. For example, if you are seeking subjects for a stasis dermatitis trial, you search the prescription drug database for patients using graduated compression stockings. You can contact subjects in your database individually, or you can automate the process. You may have the capability of emailing potential subjects. If you already do this for appointment reminders and have the appropriate privacy and security features in place, it makes contacting potential volunteers efficient and convenient. Interested candidates can then be individually interviewed in detail for their eligibility. You may also have a practice newsletter or website or a social media feed which regularly posts upcoming studies. Your patients or previous volunteers can peruse these at their leisure.

You can also consult colleagues in the same specialty or related specialties. For example, a study of molluscum contagiosum may enroll subjects from referring pediatricians, primary care physicians, gynecologists, urologists, and infectious disease specialists. For a post-herpetic neuralgia study, you might consider leaving flyers at the emergency department, at pain clinics, and with neurologists, otorhinolaryngologists, and ophthalmologists. You can talk to referring physicians directly and individually to make them aware of a particular study. You can also build your reputation. You can make it known that you conduct clinical trials in dermatology in general or perhaps in a specific area of dermatology, for example, skin cancer. You can let your colleagues know that if they have patients who may benefit from a trial to have them contact your site to see if anything is ongoing. You can give talks on the studies you have done or are doing. Ask permission to leave study handouts or flyers. Since you are a busy physician and investigator, you know how busy your

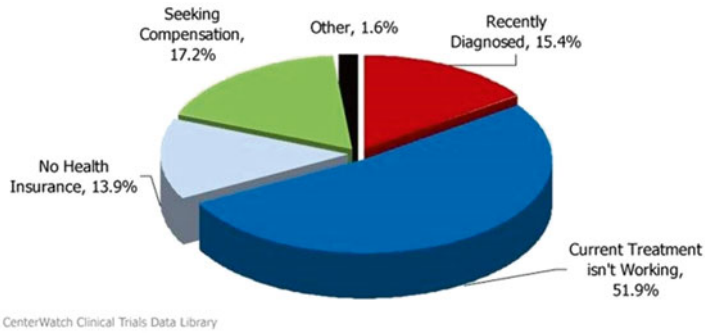

Fig. 5.7 Reasons patients seek online clinical trials information. *Source*: CenterWatch Survey of 935 Online Clinical Trial Information Seekers, 2010

fellow colleagues are. If your colleague makes a referral, make it easy for him or her. Make sure you or your staff does all of the legwork to get a potential subject interviewed or seen with minimal or no hassle on the part of the referring physician. Remember, they're the ones doing your site a favor.

You can identify patients from your own practice, from colleagues, from databases, community support groups, and advertising (with IRB-approved materials). You can use EMRs or lab data. For example, the U of S. Carolina screened 7.3 million laboratory values from 69,000 patients, to identify 70 who met automated criteria. Of those 70, 3 ultimately participated in the trial. Because of privacy, if you can't contact patients directly for studies, but you can contact their treating physicians, who can then talk to the patient to see if they would like to participate in a trial.

The factors behind subject recruitment have been studied in detail. Most subjects volunteer for altruistic reasons (Fig. 5.7).

The hurdles to recruitment are many and growing, but the most common are increasingly strict inclusion and exclusion criteria.

Incentives for subjects participating in a study:

- Access to expertise normally not available.
- Closer medical monitoring.
- Extra TLC and support.
- Help others learn more about your disease.
- Help yourself learn more about your disease.
- Income (response of 34 % of volunteers).
- Free medication and medical care (32 %).
- Altruism (76 %).

Barriers to participation in a study:

- Criteria too strict.
- Protocol too cumbersome.
- Politics (rival hospitals, researchers) preventing referrals.
- Bad publicity about the dangers of clinical trials.

- Investigator/hospital fear of liability.
- Insurance may not pay for any care for a patient in a protocol.

Most referring providers and staff in the healthcare community refer with altruism as their primary motivation, providing finder's fees is not suggested. You can offer educational dinners, where you can discuss with your local providers the study criteria and give people pocket cards with study information on the front and inclusion/exclusion criteria on the back. If you are looking in the hospital or other clinics for potential recruiters, secretaries, transcriptionists, and unit coordinators are the best people to approach with leaflets and flyers.

It's important to have a good rapport with the patient. Ask patients if their PCP wants you to inform them of a study. Emphasize it is a study with new medication that is not yet on the market. Explain that every medication on the market has gone through the same phases of study. First it's tested in animals, then healthy subjects, third on patients who don't have many other problems. Fourth it is given to patients with more complicated underlying illnesses. Explain why it is important to develop new medicines. Put the drug in perspective with any similar drugs on the market. Explain risks first, then benefits. Decide if it's a medicine you would take or recommend to a family member in the same situation. The latter is a good threshold for not being coercive, especially for indigent patients.

5.17 Informed Consent

This is the core of every study, and failure to understand it or implement it properly carries huge penalties. The sponsor often provides a template consent, but many investigators write or modify their own. These may suit the investigator's particular population. The difference between a consent and a contract, is you can opt out of a consent at any time without penalty. The consent should be simple, direct, and clear. Use straightforward language like surgery instead of procedure. Don't use language that minimizes negative consequences.

The consent form. This is a critical document central to clinical research. It is based on one of the three ethical principles of the 1979 Belmont Report on the Ethical Principles and Guidelines for the Protection of Human Subjects in Clinical Research (http://www.hhs.gov/ohrp/policy/belmont.html), the principle of respect for persons. Informed consent allows subjects to make an informed and voluntary decision about whether or not to participate in a study. It has eight required elements and six optional elements as discussed in 21 CFR 50.25. The required elements consist of a research purpose statement, foreseeable risks, benefits, alternative treatment options, confidentiality statement, medical treatment or compensation options, and contact information. Additional elements include currently unforeseeable risk, the termination of subjects without consent, additional costs, consequences and procedures for withdrawal from the study, and new findings of the study. Individuals who are consented must understand the risks and benefits of a study, and must have the ability to make a

reasoned judgment about their participation. If individuals who have an illness or disability cannot give consent, they can still participate if their legal guardian is able to provide consent on their behalf. Subjects must be consented before any study-related procedures are performed. It can even take place before screening if procedures are required to determine eligibility. In some studies, there are two informed consents, one for screening, and one for enrollment. Some studies bundle screening and enrollment consent into one document. Informed consent is not a contract, it is a consent. Subjects can withdraw consent at any time without cause. It is not just a document, but an ongoing interaction between the investigator and the subject that matches the duration of the study. Informed consent can be administered by the investigator or study coordinator. It should discuss the purpose of the study and any procedures done. It should cover risks and benefits. It should reveal potential conflicts of interest of the investigators. It should discuss subject compensation. It should clearly let subjects know that there is no penalty for nonparticipation. It should spell out that subjects may withdraw consent at any time for any reason or no reason.

Standard written consent is required for any face-to-face research activity in which risk to subjects is minimal or greater. A waiver of documentation consent, or verbal consent form still requires consent but does not require subjects to sign a form. It is used in minimal risk research, for example, internet surveys, or phone interviews. Waiver or alteration of the requirements for informed consent occurs when research is conducted without getting study subject consent. This may be used in medical chart reviews or analysis of existing data.

Informed consent may be waived in the following scenarios: you may get emergency exemption from prospective IRB approval for investigational drugs, devices, or biologics if the patient has a life-threatening condition (such as Stevens–Johnson Syndrome) or a severely debilitation condition which could cause irreversible morbidity (such as a limb-threatening vascular crisis), and there is no standard acceptable treatment available for the patient's condition, and there is no time to obtain IRB approval. Such an occurrence still needs to be reported to the IRB within 5 business days, and any subsequent use of such a therapy requires following IRB review and 21 CFR 56.104(c). You may also get an exemption for planned emergency research. Examples of drugs include HemAssist, a blood substitute made by Baxter, and devices include placing automatic defibrillators in public sites and comparing outcomes to control locations. Treatment of subjects in emergency situations, community notification and public disclosure are required for these types of studies. The final type of waiver is the Executive waiver. The President of the United States may waive informed consent for military personnel to receive an investigational product.

Elements of the consent include:

- A statement that the study involves research.
- The purpose of the research.
- A detailed description in layman's language of the study procedures.
- The time frame.
- Anticipated risks, discomforts, and inconveniences of the study.

- A reasonable description of potential benefits.
- Alternatives to participation in the study.
- Confidentiality statement, saying who will have access to records, specimens, photos, and tissue and for what purpose.
- An explanation of compensation for treatment and compensation for any adverse events.
- Contact information for questions including the site, the PI, and the IRB.
- Declaration that participation is voluntary, that no benefits will be lost if subject chooses not to participate, and that there is no penalty for early withdrawal.
- Subject may be dropped without subject's consent should PI or sponsor decide it is in the subject's best interest, or should the study be terminated early.
- A description of any costs the volunteer may incur.
- A note that the subject will be apprised of any new findings that are significant which might affect the subject's decision to continue in the study.
- A note that the volunteer has received a copy of the informed consent.

Make sure it is written at the fifth grade level. You can find sample consents from the University of Michigan, and the University of Southern California. You can also do your own SMOG (Simplified measure of gobbledygoop) test or run your text through a SMOG readability calculator at: http://www.readabilityformulas.com/free-readability-formula-tests.php.

Some consenting tips for you:

1. The patient must personally sign and date the consent form.
2. The patient must receive a copy.
3. Document all of the consent process in the medical record.
4. Keep a second copy of the informed consent at a separate location.

If patients withdraw consent for therapy, ask if they will still allow use of their data and contact information for limited telephone or email follow-up. Subjects can withdraw permission to use their blood or tissue. HIPAA prevents their lab results from being in the patient's chart, so they don't lose insurance for an abnormal finding.

5.18 Advertising: Must Meet FDA Regulations, and IRB Approval

You may need to consider advertising. All advertising must be approved by the sponsor and the IRB, and you need to have a budget line item for advertising. Some sponsors will approve an advertising budget, and some will not.

All advertising and patient educational materials should be in the regulatory binder.

You will have to decide which type of media would best serve your needs (traditional media such as radio and television, or nontraditional media such as the web and social media). You will need to sort this out in advance. If you feel you have an adequate study subject pool between your own internal database and referrals from

colleagues, you won't need to advertise. However, if the study has unique requirements (for example, a phase I trial of healthy subjects requiring an overnight stay and frequent blood draws), or is of a rare disorder (for example, junctional epidermolysis bullosa), has a potentially significant dropout rate (for example, a year-long study of a psoriasis medication vs. placebo on subjects with a high PASI score), it is less likely to draw enough volunteers without advertising. You may also need to budget more staff time for difficult studies, because your staff will be working harder to recruit subjects, and working harder to give subjects the TLC they need to stay in the study, especially if they have a skin condition which significantly affects their quality of life, and are on a placebo arm. Your sponsor may engage a media/advertising firm to help all study sites with advertisement, or you might be given an option to advertise on your own.

Bigger investigational sites have their own internal resources (advertisement coordinator) responsible for advertisement creation and submission for Sponsor and IRB approval.

Advertisements (including television, radio, newspaper, poster, handouts, flyers, leaflets, websites, email invitations, text or social media invitations, pertinent press releases, and interviews if they pertain to a study). All such recruitment materials must meet certain guidelines for IRB approval. They must use the word research to make it absolutely unequivocal to potential subjects that this is an investigational study. Subject eligibility criteria should be outlined (for example, adult males over age 18, or females of non-childbearing potential). You have to mention if subjects will be paid for participation, but the amount is not necessary to include in the recruitment materials, but it should not be excessive, and it should not be the most prominent feature of the notice. Some Sponsors or IRBs would not allow the amount of compensation in advertisement materials.

According to FDA guidance for IRB and Clinical Investigators (Fig. 5.8),

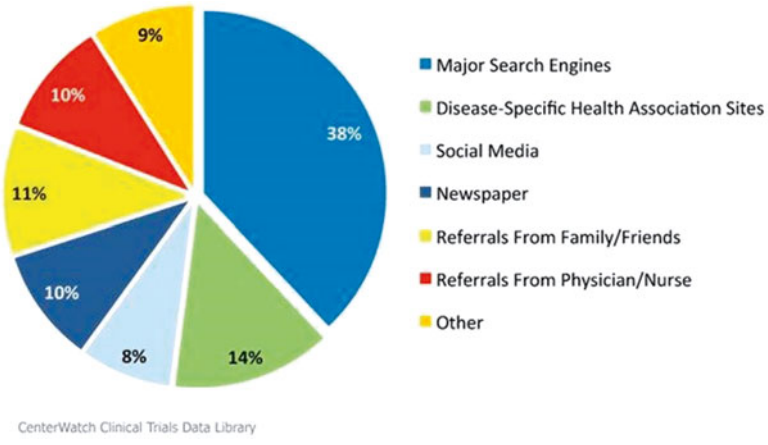

Fig. 5.8 Methods used to search for clinical trials. *Source*: CenterWatch Online Patient Survey 2012–2013; $N = 858$

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the database system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study. When such advertisements are easily compared to the approved consent document, the IRB chair, or other designated IRB member, may review and approve by expedited means, as provided by 21 CFR 56.110(b)(2). When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

FDA expects IRBs to review the advertising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence. [21 CFR 50.20, 50.25, 56.111(a)(3), 56.111(b) and 812.20(b)(11).]

When direct advertising is to be used, the IRB should review the information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting subjects is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. The IRB should review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape. The IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB may wish to caution the clinical investigators to obtain IRB approval of message text prior to taping, in order to avoid re-taping because of inappropriate wording.

No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also be a violation of the Agency's regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and of investigational devices [21 CFR 812.7(d)].

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" leads study subjects to believe they will be receiving newly improved products of proven worth.

Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest.

5.19 Web Advertising

Over the past decade, the Internet has gained credibility as a viable study subject recruitment resource. Web advertising has tremendously grown and is becoming a most popular recruitment venue. In 1999 a survey was conducted by ACRP, which found that 15 % of clinical research professionals were routinely using the Internet to recruit study subjects, by 2001 almost half of surveyed researchers were using web advertisement and in recent years it has become a main advertising venue.

Some websites provide general information. MGH has a video titled: Entering a Clinical Trial: Is It Right For You?

Social networking sites specifically aimed for advertisement of clinical trials include: Click It Forward, Inspire, Medici Global, Inclinix and PatientsLikeMe.

There are an increasing number of clinical trial search services, either run as standalone businesses or as additions to existing ones. One new clinical trial search engine launched in April 2013. MyClinicalTrialLocator.com aims to make it easier for patients to find studies and to help researchers recruit suitable trial participants, largely by making publicly available information from the US government's clinicaltrials.gov site more user-friendly.

Another similar service, TrialReach, bills itself not as a clinical research company but as an internet one and says its goal is to "democratise the information and access to medical research." To help it achieve this, the company recently partnered with Patient.co.uk, a leading UK health information website, in a deal that will greatly expand access to TrialReach's clinical trial search tool.

A yet-more advanced model is that developed by online community PatientsLikeMe, which built its audience first and then expanded into clinical trial search. PatientsLikeMe this year signed up Sanofi and inVentiv Health as clients for its clinical trial search tools to match patients to studies.

5.20 Monitoring

Monitors (CRAs) tend to visit monthly. They typically audit source docs to verify inc/exc criteria, and collect data on AEs. They will also look for data accuracy. They will look into recruitment and offer tips on enrollment. Any discrepancies will be reviewed with the study coordinator (CRC). Clinically significant ones will be reviewed with the Principal Investigator. Monitors will also review regulatory documents, informed consents, screening, and enrollment logs. They account for IP and documentation. Any monitoring findings will be discussed in the follow-up letter.

5.21 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

IND safety reports. The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drugs under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for

reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

Serious and unexpected suspected adverse reaction. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

(a) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens–Johnson Syndrome).
(b) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
(c) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical.

For more info: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32.

5.22 Record Keeping

This is a crucial part of your study. There are a number of records which need to be maintained, updated, and stored throughout the course of the study and well after your part of the study has been completed. Organization in record keeping can make your study visits go more smoothly, save you, your monitor, and your sponsor money, and make compliance, audits, and inspections less cumbersome. One of the key documents for each study is the Regulatory Binder.

5.23 Regulatory Binder

Your study should have a regulatory binder. This should contain all essential documents. The ICH GCP guidelines specify that all essential documents allow anyone to evaluate the conduct of a trial and the quality of its data. It's often the first thing monitors or auditors look for during visits or audits. A good way to organize the binder is to group Pre Study Documents in one section, Study Documents related to the actual study in a second section, and Post-Study Documents, which are generated after completion of the study, in a third section. The binder may be in one

single binder in one place, or divided in several binders in one or more places. Synonyms for the regulatory binder include: study files, investigator files, or investigator binder.

As the name implies, regulatory binders hold all regulatory documents in one place. You'll want to make sure your regulatory binder is set up properly, and the study coordinator knows how and why to maintain it. These binders are often provided by the sponsor or the drug company. Typical contents of regulatory binders include:

- Signed protocol and amendments.
- Investigator's brochure.
- FDA 1572, CVs for all personnel listed on this form.
- Approval letter from IRB and all IRB correspondence.
- All IND safety reports, and acknowledgement of receipt by IRB.
- Site safety reports to IRB.
- Informed consent and advertisement approval by IRB.
- IRB member roster.
- IP inventory, shipping logs.
- Phone logs.
- Lab certification, lab normals, lab reference ranges.
- Study closeout letter.
- Visit logs for CRAs to document their visits.

The regulatory binder includes documentation of site personnel education and training. For example, personnel involved in human subject research are required to have HIPAA training and human subject research training. This can range from basic human subject courses to human subjects protection training, to good clinical practice courses, depending on the staff member's qualifications and level of training. The nature and currency of the training should be documented in a training log. The site initiation visit can be included in the training log.

A delegation of authority log lists the responsibilities of each member of the research team. It lists the dates of their involvement in the study, and requires their signature and the signature of the principal investigator. The site personnel signature log is a document that can verify staff initials, signatures, and handwriting samples.

There should be a section which includes investigator CVs and FDA forms. Investigator curriculum vitae should be current over the past 2 years. Professional staff licenses should be included and up-to-date. DEA certificate information should be included and current if required for the study. FDA form 1572 should be included in this section and form 1571 if this is an investigational new drug. These forms can be found on the FDA's website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm.

You should have a section for a screening log which includes subjects who were screened, the subjects who did not meet enrollment requirements, and the reasons for screen failures, if applicable. If subjects fail screening, be sure to ask if they can be rescreened. You can also include a subject tracking log, which tracks visits for all

subjects enrolled in the study, reasons for early termination, and makes sure patients keep their visits as required by the protocol. Consent forms should be included in all their forms in reverse chronological order, with the most recent approved consent form first. You can put the most current version in a plastic folder for ready access. All amendments to the consent form must be approved by the IRB, and this approval must be documented and included in the consent section. HIPAA forms should be included in the regulatory binder. All versions with IRB approval should be in the HIPAA section.

The protocol should be in the regulatory binder. Any amendments should be placed in reverse chronological order, with the most current version first, and in a plastic sleeve for ready access. Each amended version should be stamped with IRB approval.

There should be a section for IRB approval and correspondence. It should contain the original application for IRB approval. It should contain IRB approval letters. IRB approval letters can be provisional (or contingent), and final. Both types should be included in this section. Any correspondence with the IRB, including emails, should be in this section. The composition of the IRB should be in this section. Protocol amendments and modifications, interim evaluations such as data safety management board reviews, and continuation reviews should be included. Final study reports and close-out reports should be here.

You should have a tab for the investigational product. This can include all versions of the investigator's brochure. You can have a separate investigator's brochure as long as you include a page referencing its location, and versions received. You have to document submission and review of all versions sent to the IRB. If you have an FDA-approved drug, include a copy of its package insert. If you are studying a device, include a manual describing the device.

If the study is terminated, or if a principal investigator is leaving, notify the sponsor (if applicable), and the IRB.

Protocol deviations and protocol violations should have their own section. All documents related to deviations and violations should be stored in reverse chronological order in this section, with the most up-to-date versions at the top. Any correspondence or communication with the sponsor regarding deviations and violations, including emails and telephone conversations, must be documented and included.

Protocol violations reflect any changes to or departures from the protocol which are under the control of the investigator and have not been approved by the IRB. There are two categories of protocol violations: major and minor.

Protocol violations must be well documented and reported. These are violations which affect subject rights, safety, or health. Major violations can be those that cause subjects harm, or increases their risk of harm. For example, if investigational site staff overdose a patient on an intravenous medication such as infliximab, a major violation has taken place. If the violation significantly impacts the subject's clinical or emotional status, it is a major violation. They may also be those which affect the completeness, accuracy, or reliability of the study data. If the investigator willfully engages in misconduct, it is a major violation. If there is any noncompliance with federal, state, or local law or regulations, it is a major protocol violation.

Examples of major protocol violations including enrolling subjects who don't meet inclusion and exclusion criteria, failure to obtain informed consent, and failure to adhere to safety procedures.

Minor protocol violations are those that don't cause harm to subjects, don't affect their clinical or emotional status, don't alter the completeness, accuracy, or reliability of data, and are not a result of deliberate investigator misconduct. Examples of a minor violation are failure to weigh unused study drugs, performing an eczema area and severity index (EASI) evaluation 1 day outside a study window.

Any correspondence regarding violations, deviations, and incidents should be kept in the regulatory binder.

Storage temperature logs should follow the protocol and GCPs. Examples of logs are included.

Investigational Test Article section should have all shipment records with appropriate signatures from the site and notification to the sponsor of receipt. Site accountability records should contain an inventory of the drug or device and allow personnel to know when additional supplies are needed. Subject Drug Accountability Records or Device Log notes the date and quantity of the drug or device dispensed to the volunteer and the amount returned. For blinded trials, Blind Break Instructions which specify conditions and procedures for unblinding study drug can be in this section.

Lab Certificates/Reference Ranges. This section should have a copy of current certifications of all personnel involved in each lab listed, and their reference ranges. The CV of the lab director should also be included.

A separate correspondence section can include communications from the sponsor, the CRO, or the monitor. If the study has newsletters, these can be included in this section.

You should have a blank CRF in the regulatory binder. If you are doing eCRFs, you may print a blank CRF to include in the binder.

If you or the sponsors have notes to file, create a section for this. Notes to file can be made as needed. They should be legible if they are written by hand. They should be signed and dated. They should clearly explain the issue being addressed. They should include any corrective action or follow-up.

The binder should contain a record retention matrix to dictate record retention and disposal. For the FDA, under 21 CFR 312.62, records should be kept for 2 years following FDA approval of a drug or device. If the drug is not approved, they should be kept for 2 years after delivery or investigation of the drug is discontinued and the FDA is notified. Sponsors may have additional requirements for record retention.

Other types of records may have different retention requirements. For example, conflict of interest records under 42 CFR 50.604 and IRB records under 45 CFR 46.115 and 21 CFR 56.115 need to be kept for 3 years after submission of a final report. HIPAA records need to be kept under 45 CFR 164.530(j)(1) for 6 years from the date of creation. Research misconduct records under 42 CFR 93.317 need to be kept for 7 years after the completion of any misconduct allegation. Retention of records for pediatric studies may be for 7 years after the child reaches the age of maturity.

5.24 Drug Storage and Accountability

The stringency of accountability matches that of narcotics. Each dose must be counted. There should be a chain of custody for the investigational product. Transfer from the company, to the site, to the patient, to return of unused medication to sponsor, must be meticulously logged. The medicine must be stored in a secured area. Access must be limited to authorized personnel. Temperature (humidity and light in certain cases) need to be controlled, tracked, and logged. If the study drug is in a pharmacy dispensing other medication, it has to have a designated area, clearly labeled, reserved for investigational drugs.

You should include a log to track samples which should have a clear chain of custody from sample collection to labeling, storage, packing, and shipping. You should also include any training of the involved personnel, including certification on shipping training. Any receipts can be placed in this section, or in individual volunteer files. Remember that biological specimens must comply with FAA and IATA rules on hazardous materials.

Develop a system or tickler file (Consider Organizing from the Inside Out by Julie Morganstern) to identify or mark send-out kits, because they can become outdated. Be sure to check with the pharmacy prior to holiday periods to make sure there is no shortage of study drug.

5.25 Keeping Volunteers Happy and Subject Retention

The longer the study, the harder this is. The industry standard for noncompliance and dropout is 25 %. Continuity of care and attentive service to your subjects can reduce this percentage. Studies have shown that the biggest source of dissatisfaction for subjects is the limited amount of contact with the PI. Only 5 % of physician investigators routinely see their patients during studies. Some wags have joked that PI stands for "practically invisible." This is less often the case in dermatology studies, where a physical examination by a board-certified dermatologist investigator is often required at each visit.

You can take many small but powerful steps to improve study subject retention.

- Cluster study patients together in groups. They can provide one another with support. You have to be careful in studies where blinding and randomization are critical. In these cases, subjects may quickly learn if they are on drug or placebo, and not only compromise the integrity of the study, but drop-out, convinced they are receiving placebo.
- Provide support and small comforts (a snack after a blood draw while waiting for the next stage of the study).
- Provide transportation (especially helpful for caregivers of children and the elderly).

- Provide convenient and flexible follow-up times (evenings/weekends) to prevent job conflicts.
- Make house calls for follow-ups (especially elderly and disabled patients). You must have Sponsor/Protocol Approval if you need to make a *House call*.
- Make a convenient location available to subjects.
- Provide childcare. Many grandparents and retirees take on childcare duties and might appreciate on site babysitting during study visits.
- Try to address minor healthcare questions for subject convenience. If you are doing a psoriasis study and a volunteer has a question about acne, don't brush it off. As long as the protocol does not prohibit it, offer what advice you can about the acne and offer to prescribe medication if feasible and reasonable.
- Communicate with PCPs. With participant permission, let their primary care physician know that their patient is in a trial. Not only is this common courtesy, the primary care physician may appreciate your help, and may reinforce the importance of continuing a trial to completion. Furthermore, if he or she has other patients who might be suitable for your study, you may get additional referrals.
- Call patients at set intervals for feedback. This validates subjects' feelings and makes them part of the study team. It also is a good early warning system for detecting and addressing problems.
- E-diaries; these improve compliance (if they are left blank, a call center can call the volunteer to address any concerns).
- Be mindful of waiting times. Try not to overbook your clinic, and try to be on time. More than one subject has dropped out of a study because long waits made scheduling the rest of their day too unpredictable to continue.
- Be courteous, and appreciative.
- Treat patients like VIPs.

Often volunteers are given too much information at each visit. You can simplify this information with a simple handout. You should use a template for patient instructions. You could make a wallet card for easy reference for long-term studies. Have your contact information on the card, so PCPs call you before telling patient to quit the drug. Instructions should have at a minimum:

- Name of the medication.
- Reason for use.
- Dosing and scheduling.
- Special storage requirements.
- Medications not to be taken with trial medication (MAOs, antacids, etc.).
- Foods to be avoided (grapefruit).
- Reminders to return any unused medication and packaging, including empty packages.
- Reminders not to share the medication.
- Reminder to store medication in a secure place.

5.26 Project Management Tips

A clinical trial is a big undertaking. There are some large, and many small details which overlap in an intricate schedule to keep a trial running smoothly. Project management techniques can help you stay on top of all the details in a clinical trial. Program Evaluation Review Technique (PERT) and Critical Path Method (CPM) are techniques used to manage complex projects. Both models break down a complex project into small subunits, which are then prioritized in terms of importance. Tasks are graphically depicted on PERT charts or CPM charts or GANTT charts. Successful project management helps avoid surprises by identifying bottlenecks such as:

- Availability of unusual piece of equipment
- Special training needed by a staff member

Details. When you design your project, think about details. For example, if you have to send specimens to a lab, ask yourself:

- Where can I get dry ice? How often? What about holidays and weekends? How soon after ordering?
- Is there enough storage for drug supplies, big-box send-out kits, and CRFs (which need to be stored forever)?
- How accessible are labs (X-ray, phlebotomy)? Is the laboratory open after-hours?
- Is shipping with a vendor? What are their hours? If they only come at 9 a.m., do specimens have to sit overnight?
- Can the shipper handle bio hazardous materials?
- Has your site met OSHA and HIPAA guidelines and training standards?
- What is the turnaround time for labs? How are you notified of critical values? Are some tests run in duplicate (hospital lab and central lab)? Who pays for duplicate testing?

You can do this on a GANTT chart, which depicts tasks on one axis plotted against time. You can sketch this on graph paper, and later use a GUI or time chart on Excel. The PERT-CPM model is more complex but shows which tasks are dependent on others. There is software designed to help with project management. If you have a large site, you can use computers to manage a variety of study logistics including patient scheduling, drug inventories, and tracking reg docs and grant payments. Examples include: Study Manager by Advanced Clinical Software, TrialWorks, Oracle SiteMinder, open-source OpenClinica, DDOTS (Data Doctor Office Technology Systems) CREDIT (Clinical Research Environmental Data Informatics Tracking) for patient communications, billing, and IRB activities.

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Chapter 6
Budgets and Contracts

Ella Grach

Each study is different. Each investigator and investigative site is different. Each relationship between the various aspects of the clinical investigative team, from the investigator, to the staff, to the facility, to the laboratory, to the pharmacy, to the sponsor, to the legal and administrative teams, to local and regional regulatory bodies is unique. The way in which you address these relationships depends upon your background, experiences, and resources. The more familiar you become with the details of these relationships, the better you will be able to navigate and negotiate them. Central to these relationships are some critical documents and processes. These include the protocol, a budget, and the clinical trial agreement, or contract.

6.1 Protocol

The protocol is a standard document composed of many key elements. Protocols need to have a title which includes its phase (I, II, III, etc.), its design (randomized, double-blind placebo-controlled, etc.), if it is multicenter, the investigational drug, the target disease (i.e., plaque-type psoriasis), and its stage (moderate-to-severe or refractory to PUVA).

You will likely have to sign a confidentiality agreement before you can review the proposed protocol. When you are deciding if a protocol is feasible, you will have to do so from two major points of view: scientific feasibility and ethical feasibility.

Scientific feasibility: Does the study make sense based on the disease and its mechanism? Are its objectives clear or vague? Do the objectives align with the study design? Are appropriate data being collected?

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Ethical feasibility: Is access fair? Are some groups unnecessarily excluded? Are the safety/efficacy end points reasonable? Is the risk-benefit ratio reasonable? What are the plans to minimize risk? Does the design fit the standard of care in the community (melanoma vaccine trial)? Is the washout period difficult or hazardous? What happens at the end of the study? Will they have continued access to a drug they can't otherwise afford?

The protocol should have the names and contact information of all investigators, co-investigators, sub-investigators, and biostatisticians.

The protocol should have the generic and market name of the study drug or device. It should have an initial version date and any amended version dates.

The protocol should have a table of contents which typically contains: List of Abbreviations, Study Schema, Study Summary, Background and Rationale (including disease background, study agent background and known toxicities, other agents, rationale, and correlative studies), Study Objectives (primary objectives, secondary objectives, exploratory objectives, end points), Patient Eligibility (inclusion criteria, exclusion criteria), Treatment Plan (treatment dosage and administration, toxicities and dosing delays/modifications, concomitant medications/treatments, other modalities or procedures, duration of therapy, duration of follow-up, removal of patients from protocol therapy, patient replacement), Study Procedures (screening/baseline procedures, procedures during treatment, follow-up procedures, time and events table, removal of subjects from study), Response Criteria (safety, tolerability, efficacy), Adverse Events (experimental therapy, adverse event monitoring, definitions, steps to determine if an adverse event requires expedited reporting, reporting requirements for adverse events, unblinding procedures, stopping rules, Drug/Device Information, Correlatives/Special Studies (sample collection guidelines, assay methodology, specimen banking), Statistical Considerations (study design, study end points, sample size and accrual, data analysis plans), Study Management (conflict of interest, IRB approval and consent, required documentation, registration procedures, data management, monitoring/auditing (all studies require oversight and monitoring to ensure participant safety and data integrity; the degree and frequency of monitoring should match the complexity or risk of the trial), adherence to the protocol, amendments to the protocol, record retention, obligations of investigators), References, and Appendices.

Site monitoring visits ensure that the well-being and rights of human subjects are protected. They check that acquired data are accurate, complete, and verifiable by source documents. They make sure that the trial is compliant with the protocol, with GCP and all other guidelines and regulatory requirements. Make sure you are ready for your monitors and that you give them the space and time they need to do their job.

Some studies, particularly those under CFR 46.111(a)(6) and 21 CFR 56.111(a)(6) for complex diseases or toxic therapies may require independent safety monitoring by a safety officer or data safety monitoring board to periodically review the trial and determine whether it may continue or require amendment. A data safety monitoring board is a team of clinical trial experts, biostatisticians, bioethicists, and disease experts who provide oversight for trials with a moderate to high risk. For example, a trial of IVIg in the treatment of toxic epidermal necrolysis would

likely have oversight by a data safety monitoring board. Such oversight would involve a data safety monitoring board staff, the investigator, and the study site staff to meet twice annually or more often to review the study for safety, adverse events, unanticipated outcomes, and efficacy. The DSMB reviews the protocol, and evaluates the progress of the trial, data quality, and participant safety. They listen to problems reported by the PI and assist in resolution. They make recommendations regarding continuation, termination, or modification of the trial. The data monitoring safety plan would have clearly defined rules on outcomes which would dictate early termination of the study, or early withdrawal of subjects from the study.

6.2 Budget

A contract or clinical trial agreement tells you what and how you will be compensated for performance of trial. If you don't account for an expense in the contract, it won't be paid. If an unexpected expense comes up, and is not in the agreement, you need to amend the contract, negotiate the payment, and sign the amendment. Contracts fit into a larger picture of clinical research (Fig. 6.1).

You need to budget consistently. If your consent form states that a skin biopsy will be done, and there is no reimbursement for a skin biopsy in the budget, you will not be reimbursed. The informed consent should not state the subject's health insurance or the subject will be responsible for the cost of the biopsy if it is study related.

You have to capture every possible expense related to a trial and account for it in the billing and budgeting process. If you don't, it could hurt the financial viability of your investigative enterprise. Obvious expenses include all the procedures listed in the protocol flow chart. You should look at this carefully because there may be

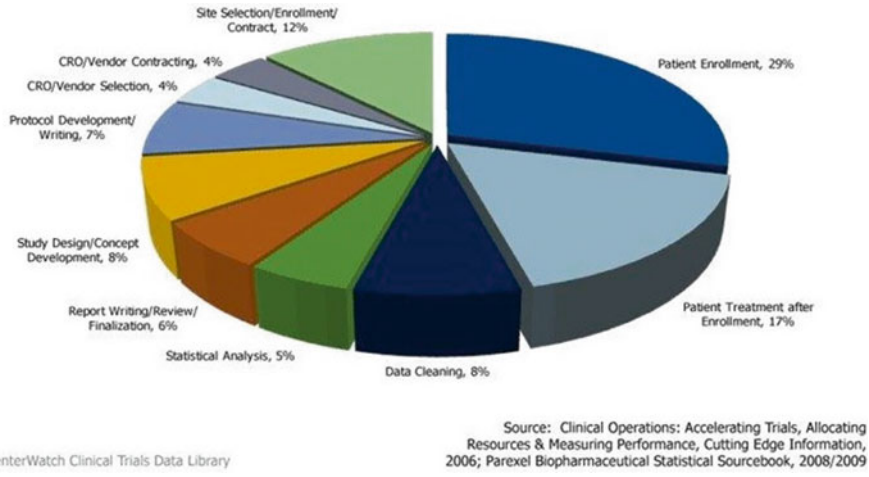


Fig. 6.1 Various clinical trial activities

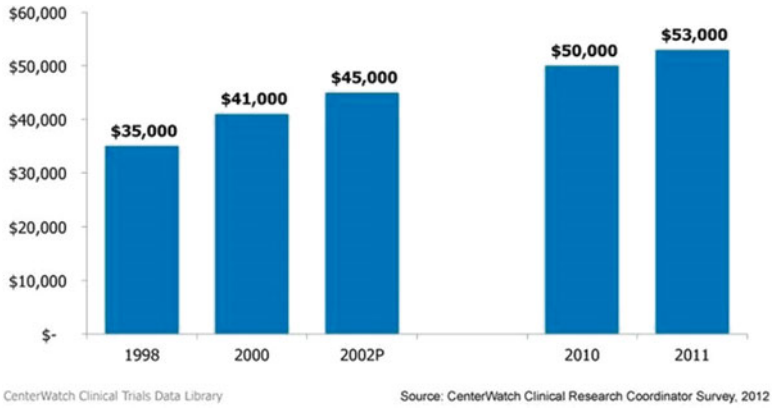


Fig. 6.2 Clinical research coordinator salaries (median annual salary, US$)

implied costs. For example, if the laboratory costs of a urinalysis and electrocardiogram are reimbursed, but the staff time for collection of the urinalysis or administration of the cardiogram are not reimbursed, the oversight needs to be addressed. You have to consider protocol-related items outside the study table. For example, if a specimen needs to be shipped, all shipping costs should be covered. If the shipping requires special containers or dry ice or overnight delivery, supplies and costs should be provided.

You have to think of your costs before you start the study. For example, you may need to budget your preparation for the study, your IRB fees, your setup costs for labs, radiology, and pharmacy. You can itemize these as start-up fees. You need to build in costs for the financial management of a trial, including your billing compliance costs (particularly if you use a clinical trial management system). You have to factor in end-of-study costs, such as storage of study documents and preparation for possible auditing.

It's also important for you to determine how you will get paid. The timing and details can be a source of friction between investigative sites and sponsors (Fig. 6.2). There is often a long gap between committing your time and effort to being awarded a study to getting your first payment. Negotiating a first payment or an early payment (start-up payment) can help you with start-up costs so that you can support your staff in setting up the trial, completion of IRB submissions, reviewing your subject's database and pre-screening patient's medical records for eligibility.

Be aware of the costs of data collection and management. Data may be collected on paper source documents and then submitted as paper or electronically via an EDC (electronic data capture) software system. While electronic data capture saves sponsors money, it takes extra study site time for data entry. There is no standardization. Your site will have to learn a different system for each study it participates in. The training time, and the time to enter data may cause your site to lose money simply on data collection and data entry. There is an effort to standardize EDC systems, for

example, through the Clinical Data Interchange Standards Consortium, but until then, the panoply of software costs investigator sites staff time, money, and work.

Delays take time. Be sure to budget for them. One source of delays could be a use of "local" hospital or academic IRBs. Another is the budget and contract negotiation process, especially if it involves multiple parties, such as the investigator, CRO, billing department, IT, legal department, lab vendors, shipping vendors, and insurance providers (if applicable). This is especially true for large institutions. For example, at university sites, contract approval may require 20 steps and 13 decision points; and a community site may require much less time and have less steps. The fewer steps and fewer decision points, the faster contracting and budgeting can move forward. To start a cancer study at academic institution, the average start-up time is around 180 days, with about 100 days going toward negotiation. These times can be longer in Europe (200 days) and Asia (270 days). They are shorter in the USA for a central IRB (37 days) vs. a local IRB (107 days).

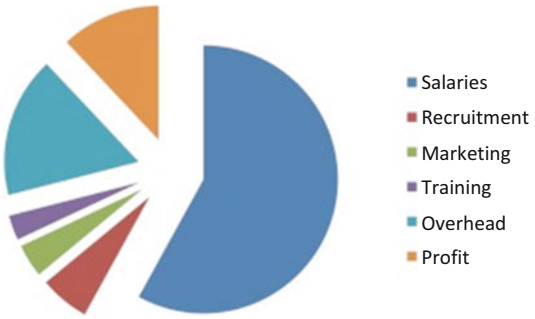
You need to know how many subjects are to be enrolled in the study. You have to take into account how many you will need to screen and how long it will take to achieve your goal. You have to see if the inclusion and exclusion criteria will alter your workload. You have to read to details of the study to see what is required of subjects. Is the study easy and straightforward, or is it laden with complex procedures and documentation at each visit requiring a great deal of your time and staff time? Are there many visits with impractical or inconvenient procedures and treatment regimens? Do the visits spill into extended hours such as nights, weekends, and holidays for which operating costs and staff costs are higher?

Laboratory costs to include in the budget are the tests and supplies and personnel time involved in obtaining specimens. You will need to include lab reagents, equipment maintenance costs, and a budget for packing and shipping specimens. If the shipping is international, you will need to budget for the extra costs and customs. If you have to store specimens, be sure to include the costs of refrigeration, alarm systems, and other back-ups.

You and your coordinator may need to travel to investigator meeting (90 % out-of-town) which could take a couple of days out of your schedule. Attendance at training sessions such as investigator meetings can be difficult. Many occur on weekends and take you away from family, but some occur during the week and may take you away from the clinic as well. Be sure to factor in the direct cost of travel and the indirect cost of lost revenue from your practice if training sessions or investigator meetings occur on one of your clinic days. Many sponsors will reimburse you for expenses of the meeting itself, but will not pay you for lost income. You should still include opportunity cost as a line item in your budget so that you can have a realistic assessment of the feasibility of conducting a trial. If your trial requires you to be away from your clinic for extended periods, and you lose a great deal of revenue in your absence, and it is not adequately reimbursed, you may have to reconsider doing the study.

Don't forget to include study start-up costs. You need to add costs for additional storage space for study product or documents. Be sure to budget extra time spent on review of data, labs, assessment of subject progress, and adverse events. Adverse

Fig. 6.3



events in worldwide studies are more time consuming to review and address. If you have a number of sub-investigators you work with, be sure you include your time supervising them and communicating with them.

The recruitment phase costs 27 % of the budget, the most expensive and difficult part of drug development ($2 billion/year) (Fig. 6.3). Recruitment has become more difficult because the FDA has tightened criteria for efficacy, and because multiple companies are looking at the same pool of potential volunteer subjects. Also, sites may need to screen 10–20 subjects to identify one viable candidate, and sponsors don't often compensate adequately for screening or screen failures.

Ask if the sponsor will help with subject recruitment. Some sponsors work with third party HIPAA compliant centralized study subject recruitment services. Ask if extended after-hours time will be required for your staff. You may also need to budget for this. If your sponsor requires special training (e.g., PASI training, electronic case report form training, special lesion counting training for the protocol), ask if this is reimbursed. Many studies also have source documents which are used to generate case report forms. Some sponsors provide them, some don't. These can be a tremendous expense. If you are responsible for providing the source documents, be sure you budget for them. Your budget should include the actual cost of the documents and the time in preparing them, as each is study specific and study visit specific. If photography is required, find out if equipment and training are furnished.

While being a novice investigator, it is very important to conduct a successful study as well as maintaining the business side to make sure that you stay profitable. I suggest that when you are reviewing the protocol, you make a checklist to answer the following questions:

- Are the number of subjects to be enrolled and timeline provided by the sponsor are realistic?
- Would you have sufficient number of patients in your practice database to enroll in the study?

- If you suspect that you do not have the sufficient number of patients in your own database; will you need to (a) advertise for patients; (b) do you need to collaborate with other practitioners in your area?
- How difficult is protocol to implement? (I suggest carefully assessing labor intensity of the protocol and making sure sufficient well-trained staff is available)
- Is proposed budget reasonable?

Most sponsors and CROs structure their budget on a fee for service basis; their proposed budget is per subject and prorated on a number of visits subject actually completes. Sponsors feel that they are contracting a service from investigator and do not expect to pay if services are not delivered. I would like to warn you about hidden cost that is usually associated with conducting a trial. For example, sponsor is proposing budget as mentioned above on per-subject basis; which does not include any study start-up activities including IRB submission; physician and coordinator time spent on initial protocol review and assessment.

The majority of the cost of a clinical research enterprise goes to staff salary.

My preferred way of coming up with a fair budget starts with careful review of the protocol required tasks and procedures including estimated time for investigators, coordinators, and sub-investigators. In addition, I take a careful look at the study required procedures: could they be all done at my clinic? Are there study procedures requiring radiology services? Please make sure to check with your local services on the cost of CT, or MRI required per protocol before signing off on the study budget. Remember to think about additional space to store the product or a need to have a pharmacist on the study. Give good consideration to extra time to be spent on daily/weekly review of each subject data, assessment of subject progress in the trial, or potential adverse events; and continuous communication with your study coordinator and sub-investigators.

- Budget: Have you done a thorough budget with a cushion for unexpected problems or delays? You should negotiate a budget and the contract details before you make an IRB submission. Sponsors don't like to discuss budgets until after you've already invested a great deal of your time. Some sponsors give you a non-negotiable budget with little wiggle room. Sponsor budgets ignore many hidden costs of running a trial (Norm Goldfarb thinks up to 80 %). Most of the time is administrative (completing CRF, reading and processing correspondence, writing and sending correspondence, reviewing charts for potential subjects). Study visits account for only 20 % of the budgeted time. Employee benefits need to be included in the budget, which can add another 30 % to base pay.
  - Include all your known fixed costs.
  - Double your normal time for seeing patients, as study subjects and documentation of the study visit require more time.
  - Estimate the number of screen failures.
  - Estimate time for meeting with the IRB and other departments and for in-service training of PIs, SubIs, and staff.

- Sponsors use PICAS (Pharmaceutical Information Cost Assessment Service) to generate budgets. The database includes procedure, institutional overhead, and personnel costs. The data are proprietary. Medidata charges are higher than PICAS. Kenneth Getz says that investigator compensation has declined 3 %/year, and work burden has increased 10.5 %/year.
- Budget will vary depending on phase of the trials. Phases 1 and 2 studies are more complex than Phase 3. You need to account for this in your budgeting.
- Negotiate in the higher range if you bring unique attributes to the study.
- Consider nonmonetary factors: investigators may sacrifice 25 % of a grant to work with a novel or innovative compound, or may bend for a sponsor with an excellent reputation, or if a compound gives your patients a unique therapeutic opportunity.

Additional budget factors to consider: lab fees, shipping and handling fees, cost of dry ice, specimen collection fees, lab bookkeeping fees, pharmacy accountability fees, administrative time (contract negotiation 2 h, legal review 1 h, meeting with pharmacy, lab, nursing, IT 2 h, protocol revisions 1–5 h), IRB (sponsor usually pays for a central IRB), radiology studies, medical evaluations (estimate 1 h initial H&P and 1 h answering subject/family questions, consent, and study order; for study visits estimate 1 h coordinator activities and 1 h for data entry, and a half hour PI time). Add a half hour for each AE if mild, and 2–3 h for each SAE. For CRFs budget 8–10 h per patient, on average, double for a complex Phase 2 trial. Add several hours for query resolutions, and 1 h per patient for record archiving.

Don't forget site sponsor meetings 1–2 h first meeting, investigator meeting 2–3 full days including travel, 1–2 h initiation meeting longer for coordinator, monitor visits 1 h PI 2–3 h coordinator, closeout visit 1 h PI 2–3 h coordinator, and audits half day for PI, 1–2 days for coordinator if in house, anybody's guess if FDA.

Start-up fees: PI time for protocol feasibility and reality testing, IRB preparation time, recruitment plan development time, screen failures.

Miscellaneous fees: patient time and travel ($25–50 typical), study marketing fee (discussing the study with local practitioners, advertising, storage, overhead, unanticipated costs (protocol amendments, high screen failure rate, changes in charges from suppliers).

There are other techniques for budgeting. For example, you can budget by activity such as: medical evaluation; administrative and overhead costs; procedural costs; and one time fees. You can budget by evaluability. There can be a line item for each evaluable subject, or one who drops out because of an AE, which is especially important for Phase 2 trials. There can be a line item for each supportive patient. A supportive subject is one who terminated early, but may be able to provide safety data.

Equipment and storage. Be sure to budget for unique equipment. This can include a setup for standardized clinical photographs. Specialized equipment needs to be calibrated and maintained. These operating and maintenance costs should be prorated for the duration of the study and should not be overlooked. If your study requires skin biopsies, include the cost of materials such as local anesthetic, syringes,

needles, specimen vials, suture, sterile surgical supplies and instruments, suture removal kits, bandages, and dressing in your budget. You may need to budget for handling, packaging, and shipping specimens. If shipments are to international locations or require specialty materials transfer agreements or IATA certified personnel, packaging, and permissions, be sure to budget for them. Have a defibrillator and medical emergency kit on site, and train your personnel in basic CPR and defibrillator use. You may need to store documents and study items in a special facility, for example, temperature controlled, having limited access, and secure. Storage costs can vary by study and can add up quickly.

6.3 Contract

Negotiating a clinical trial agreement involves multiple parties, including the sponsor, the research institute, and the principal investigator. Some of the key issues in negotiating agreements include confidentiality, intellectual property, publication opportunities, reimbursement, and liability. A successful negotiation is one in which all parties are satisfied with the outcome.

Contracts are time consuming, and full of legalese, and may be inflexible. You may want to ask for a sample contract before investing time reviewing the final version. It is stacked it in favor of the payor, especially as companies tighten their belts. Things to consider include:

- Payment schedules: tend to be at the end, while investigator expenses tend to be up front. Try to get payment as work is completed. The next best option is regularly scheduled or milestone achievement payments. Avoid withholding a percentage of the grant or otherwise delaying payment. Ask for a start-up payment with contract finalization rather than at first patient enrollment. Make sure payments include remittance advice (a breakdown of what the payments are for). If a study will require a lot of effort on your part before it begins (e.g., in getting approval from various players, or setting up equipment and facilities, or detailed contract review and negotiation), ask to be paid in advance for at least a small portion of your total contract.
- Be careful about billing Medicare and billing the sponsor for the same services. Be sure the contract describes clearly who is to be billed and under what circumstances. If a subject is injured during a study, the sponsor becomes the primary insurer, and Medicare becomes secondary. You can't waive patient copayment in the case of injury because that is considered an inducement under the Federal False Claims Act. Routine care related to the trial is then covered. Rush University in 2003 noted some double billing and came forward to Medicare with a resultant 50 % penalty and additional reporting obligations under a compliance plan.
- Avoid Anti-Kickback legislation: Start-up costs should be for time spent in submitting regulatory documents or attending investigator's meetings and compen-

sating for lost time from patient care; they should not be inducements to perform a study.

- Default: Smaller sponsors declare bankruptcy mid study. This leaves investigators in the lurch. Include a financial review of the sponsor or CRO if you're not familiar with it (current assets minus current liabilities; cash balance, history). Add the following clauses to the contract:
  - Recovery of all attorney fees and related costs, in case of nonpayment
  - Ability to withhold data from the sponsor for nonpayment until payment is received
  - Retrieval of CRFs at frequent regular intervals. If the CRFs are not retrieved regularly, the sponsor will provide the site with an interim payment for patient visits completed
  - Insurance for the sponsor, throughout the term of this agreement, and for a period of 2 years thereafter a policy of insurance covering any and all liabilities hereunder. Such insurance policy must include coverage for products liability and any liability arising out of clinical trials, including contractual liability for no less than $5 million.
- A publications clause should make clear what your rights are regarding publication, including freedom to publication of unfavorable results. For example, in 1990, Dr. Betty Dong, a clinical pharmacist at University of California San Francisco, conducted a trial on the bioequivalence of Synthroid and three other generics. When she found the three generics were bioequivalent to the brand name Synthroid, made by Boots, the company moved to block publication, and tried to discredit her when she refused to water down her study results in a publication. The university did not support Dr. Dong because of a clause in the research contract that prohibited publication without written consent from Boots.
- Patent and inventions clauses: Two dermatologists who noted the benefits of Minoxidil for androgenetic alopecia had to sue UpJohn for their rights. Minoxidil, marketed as Rogaine since 1996, generated tremendous revenue for the manufacturer. By the time Rogaine went off patent, the two were entitled $26 million in royalties (*Grant & Kahn* vs. *Pharmacia & Upjohn*). One of the new indications for brimonidine for redness related to rosacea was discovered by an astute and observant dermatologist. A careful examination of this clause will protect your ideas and keep you alert for new indications or avenues of investigation.
- Indemnification clauses should be vetted by an attorney. Never sign a cross-indemnification clause, where you indemnify the sponsor company. Insurance indemnifications clauses do not cover alleged physician error, and most malpractice insurance policies exclude coverage for clinical trials. When physicians begin to conduct research trials, it is important that they contact their malpractice insurance carrier to make sure that their coverage extends to conduct of clinical trials. If not, they should consider purchasing additional research liability insurance to assure complete coverage. Sources of coverage include Clinical Trials Reciprocal Insurance Company and Clinical Research Liability Insurance.

- Subject injury and how it is handled is crucial. In a famous case in 1999, a study volunteer named Jesse Gelsinger was treated with a novel gene therapy for ornithine transcarbamylase deficiency. Investigators at the University of Pennsylvania treated him with an adenoviral vector carrying normal copies of the gene to test the safety of the therapy. He unexpectedly died 4 days later from an overwhelming viral immune response. The FDA cited the co-investigator James Wilson of the Institute for Human Gene Therapy for several lapses: Jesse was included as a volunteer as a substitute for someone else who dropped out of the study; the university had not reported two other patients who had suffered serious side effects from gene therapy; the informed consent form did not refer to monkeys dying from similar therapy. James Wilson and the University further had financial stakes in the success of the research. Another trial with unexpected tragic consequences was the TGN1412 trial. This was a study of an immunomodulatory drug tested in 2006 on healthy volunteers. Even though the first in human pilot studies investigated low doses (1/500th the dose found to be safe in animals), it caused hospitalization of all six Phase I volunteers. Four suffered multiorgan system failure. All recovered, but one had remained hospitalized for nearly a month. The study was subsequently faulted for administering the drug too rapidly (20 min vs. 2 h in the protocol), failing to disclose possible concerns of a cytokine storm. The study led to restrictions in the UK on biologic agents targeting the immune system.
- Facilities letters: provide indemnification for hospitals. They provide indemnification for a third party not party to the Clinical Trials Agreement. Clinical Trials Agreements typically are between the sponsor and the investigator and assign responsibility for the trial to the investigator. They typically indemnify the research institution and detail payment terms to the institution. These payment terms should not violate Anti-Kickback Statutes or Stark Rules. The indemnification letters for the facilities typically bind the facility or hospital to protocol confidentiality and the intellectual property rights established by the sponsor.

Stark Law, Anti-Kickback Statute, False Claims Act

This is a federal law (42 U.S.C. § 1395nn, 42 C.F.R. § 411.353) which prohibits physicians from making referrals for designated health services to an entity with which he or she has a financial relationship. Designated health services mean clinical laboratory services, imaging services, and inpatient and outpatient hospital services. It applies to services provided under Medicare or Medicaid.

If a hospital agrees to conduct a clinical trial sponsored by a pharmaceutical company, it has to be very careful if it wishes to split research funds with you as a principal investigator if you are not a hospital employee. For example, if you are a community expert on melanoma, and your local hospital, on whose staff you serve, but by which you are not employed, agrees to conduct a melanoma trial through its cancer center, it cannot arrange for you to be a principal investigator and turn over half the research budget to you. This is especially the case if you refer patients to that hospital, or its imaging facilities, or its clinical laboratories. Instead, the hospital must determine specifically the services you will be providing as principal investigator (e.g., overseeing the study, conducting physical examinations, evaluating

skin lesions). The nature of these services should be in writing, in a research services agreement, and signed by both parties. The compensation for these services should be set out in advance and should be at a fair market value.

You, as an investigator, also have to be cautious about pharmaceutical marketing which is thinly disguised as research. If a pharmaceutical company asks you to take part in a study on an FDA-approved drug that involves minimal effort and is of questionable research value but is highly compensated far beyond market value, you may be violating the Anti-Kickback Statute 42 U.S.C. § 1320a-7b. This statute prevents willful solicitation of any direct or indirect remuneration, overtly or covertly, in cash or in kind, in return for referrals of Medicare or Medicaid beneficiaries, or the arranging, recommending, leasing, or ordering of any item or service reimbursed by Medicare or Medicaid. A violation of the law is a felony offense that carries steep criminal and civil fines per violation, imprisonment for up to 5 years, and exclusion from government health care programs.

With hospital laboratory services, you have to be careful about violations of the False Claims Act 31 U.S.C. § 3729, which prohibit knowingly filing false claims with the federal government. It also prohibits causing the filing of a false claim, creating a false record to get a claim paid, and concealing an obligation to repay monies owed to the federal government. If one of your Medicare research subjects goes to a hospital laboratory to get an electrocardiogram which is paid for by research funds of a study, the hospital may not bill Medicare for the test. If the hospital inadvertently bills Medicare for the test and is reimbursed by the sponsor or you as a principal investigator using research funds, both the physician and the hospital are in violation of the False Claims Act. As an investigator, you are required to arrange with the sponsor and hospital in advance exactly which services are covered by the study, and who will be responsible for payment. This is because sponsors like to make all payments to one party, whether it is a research site, an investigator, or a hospital. They do not typically like to make separate payments to the investigator or research facility and the hospital.

You may be paid on a per-study-subject basis. And you may receive payment in increments or milestones. For example, subjects enrolled, follow-up visits, completion of case report forms (CRFs), or electronic case report forms (eCRFs). Your final milestone may be closing out the study. This allows sponsors to encourage final submission of data, which often gets delayed near the end of studies. Contracts may deny payments for defined lapses. For example, if a subject who didn't meet enrollment criteria was inadvertently enrolled; or if a subject wasn't properly consented for the study. You may also negotiate start-up fees, administrative fees, and IRB fees. Or they may furnish the cost of a device. These have to be reasonable and not so excessive as to suggest a form of inducement or they may run afoul of the Anti-Kickback Statute, or the Stark Law, or the False Claims Act. For example, if a manufacturer of a $300,000 laser asks you to participate in a trial on the effectiveness of the laser for acne scarring, and requires you to only enroll one patient, and allows you to keep the laser, your compensation is far beyond fair market value.

6.3.1 Confidentiality

The sponsor's preference would be universal confidentiality. Large academic medical centers and teaching institutions and universities have a desire to promote research and secure the public interest, and may find onerous confidentiality clauses inimical to their mission of academic freedom. Institutions and investigators may agree that the protocol, drug, or device information would remain confidential, but that any results generated by the investigator and the institution would not be, for example, patient medical records, case report forms, and other data generated by the trial. If confidentiality is too one-sided and too ironclad, the investigator or the institution may be muzzled from publishing any findings. The confidentially of source data such as imaging and patient medical records is governed by HIPAA and state law, but not by the research agreement. Investigators will need to determine if they require prior approval to present preliminary or early stage data at medical conferences. Small offices, or clinics, or core labs may be held back more strongly by the sponsor.

Confidentiality also relates to intellectual property. If you develop any intellectual property during a trial, you retain ownership of it, unless you've expressly assigned it to a sponsor. If you observe a new indication for a study drug, or you enhance or modify a study device, be sure the contract allows you to retain intellectual property for that innovation. See if your trial agreement discusses patents and inventions related to your study drug or device. You may have a clause affording protection for the sponsor and depriving you of any patentable and nonpatentable inventions you discover during the course of conducting the trial. You may be able to allow the sponsor to own all inventions derived from the trial, and you to retain inventions related to your research methods or innovations beyond the study.

Confidentiality can sometimes be cloaked in trade secrets. Trade secrets give companies a competitive advantage. Some sponsors may want all inventions and research emanating from a trial to be labeled as a trade secret. Be careful in granting this right because it lets sponsors interfere with your publication rights. Instead, seek a publication delay to allow the sponsor time to protect the new finding with a patent, commonly 60–90 days. Sponsors may also request prior review of manuscripts 30 days before submission and the right to edit out confidential sponsor information. Sponsors may wish to limit publicity without prior approval. For example, media interviews or releases regarding a study drug or device without sponsor consent might be attributed to the sponsor.

Studies involving human subjects are risky, and can lead to subject injury or disability or death. Most contracts have a mutual indemnification clause, which protects each party the cost of a legal defense in cases where it is not at fault. For example, if a laser malfunctions and injures a subject, you may not be liable. If it malfunctions because you hooked it up to a faulty power outlet in your facility, the sponsor may not be liable. Some large medical centers and universities do not indemnify sponsors. At public institutions, state laws may prevent universities from indemnifying sponsors. Large medical centers and institutions often require sponsors to underwrite liability insurance. There is a trend toward sponsors requiring

reciprocal agreements with institutions. This is more common when sponsors deal with small hospitals, research clinics, or private physician offices.

Signatories to the clinical trial agreement are at a minimum two (the sponsor and the institution—if the principal investigator is an employee of the institution), often three (the sponsor, the institution, and the principal investigator), and occasionally more. Co-investigators or sub-investigators can sign the agreement, sign an exhibit agreement, or agree to abide by the principal investigator's obligations. Contract research organizations (see below), and core laboratories may also sign the agreement. Members of the research team who are unlikely to sign the agreement include house staff, residents, attending, study coordinators, interns, and technicians. The sponsor may, however, insist that any intellectual property developed by these non-signatories is assigned directly to the sponsor.

The clinical trial agreement is not subject to inspection by the FDA. The investigator agreement, a separate set of documents governed by 21 CFR 812.43(c), 21 CFR 812.100, and 21 CFR 812.110 require the investigator conduct the trial in accordance with FDA regulations and the protocol. These documents can be audited by the FDA.

6.3.2 Termination of the Agreement

Sponsors may terminate their contracts for convenience. They often are subject to many competing demands including budgets, other trials, feedback from regulators, and responsibility to shareholders if they are a public company. So sponsors retain this flexibility. Sometimes they also allow investigators or institutions to terminate a trial for convenience as well, though this is rare. On the other hand, investigators may not want to be forced to continue a trial if subject safety is in question. It is good to add a clause allowing you as a principal investigator to terminate a trial for cause (and this can be spelled out, such as subject safety, newly found adverse events). Some contracts let investigators to terminate agreements for any cause or no cause; the idea being an unwilling investigator may not generate optimal data.

The contract may have provisions about the principal investigator. Most sponsors look for high-profile investigators at major institutions to supervise major clinical studies. If such an investigator leaves, the sponsors may wish to move their support to the investigator's new institution, or may wish to terminate their agreement. Many sponsors protect themselves by adding a clause giving them the right to approve any replacement or substitute investigators at an institution. A lack of mutual agreement can be cause for termination of the contract.

If you are a busy investigator conducting multiple trials, your sponsor may prevent you from working on a competitive drug or device. You may find a noncompete clause. If your other studies overlap with the one in the trial agreement, you have to make the clause sufficiently narrow to satisfy your site and the sponsor.

The sponsor may request a right to inspect your site for monitoring purposes. They may request the right to visit any sites outside the clinical trial site, such as

your private office, where any clinical trial work is done (seeing subjects, reviewing labs, signing documents). They may also require notification in case of an FDA audit, and may even want to be in attendance during an audit.

Make sure that extended clinical trial agreement (contract) properly outlines the responsibilities of the sponsor and investigator including the number of subjects to be enrolled, enrollment timelines, and site indemnification language. Make sure that site indemnification survives the termination of the contract because of possibility of subject coming back a year or two later with a problem, believing that it resulted from their participation in the study. Negotiating indemnification language may be difficult and initially you may want to involve your attorney to avoid any complications.

Another important item not to overlook in contract negotiation is the subject injury reimbursement. It is customary that the sponsor will reimburse the subject the cost of treatment for injury (not covered by their medical insurance) directly caused by the study drug. It is very important that the sponsor also covers the cost of diagnosis, especially if the injury turns out not to be related to the study drug.

- Contract: Is it fair? Is the indemnification clause to your disadvantage? Is payment reasonable? Will you be paid for screen failures? You need this if enrollment is tough or the criteria are restrictive. Will the sponsor pay for prestudy expenses (site selection meeting, chart reviews) even if no patients are enrolled (as long as you can show good faith effort in the form of screening logs)? Will the sponsor pay extra for AEs and SAEs as well as audits that take more of your time?
- Pharmacy: Is a pharmacist required 24/7? How difficult is it to prepare drug?
- Laboratory: Are labs done locally or centrally? Will you be alerted to critical values? Are there parameters you can't meet, such as rapid turnaround times for specimens?
- Equipment: Will you or the sponsor provide it? What about the space for it?
- Data submission: Is it paper or electronic? Look at the CRFs to see if they make sense and to see how easy, or difficult they are.
- Monitoring: How often? Will you have visit after the first or second enrolled patient to make sure everything is going OK? Will a DSMB review your data?
- Subjective feeling: What are your impressions of the company, and their delegates? How do they handle your questions? Do they seem harried? Do they get things too late and demand things from you "yesterday"? How interested are you in the study? Is the protocol worth the aggravation or the risk? If you don't feel right, politely decline. It's much more impressive to say and mean "no" than to say "yes" and mean "no."

6.3.3 CRO

Some pharmaceutical companies oversee all of their clinical research in house. They employ their own staff to recruit investigators, conduct and monitor trials. This can be expensive and has the drawback of scalability. Sometimes the pharmaceutical research enterprise is overcommitted and doesn't have enough in house

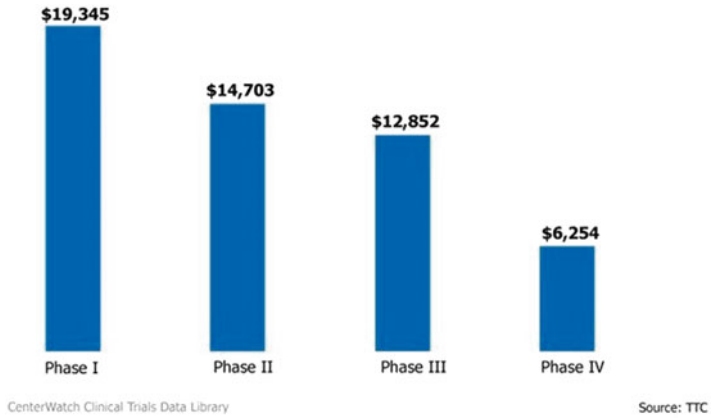


Fig. 6.4 Mean cost per patient per phase (2008–2010)

staff. Sometimes it is undercommitted and overstaffed. In an era of budget cuts, it makes sense for companies to outsource studies which can be staffed according to the needs of the study. Contract research organizations (CROs) work with sponsors such as pharmaceutical companies to outsource clinical research on a contract basis. They may be involved in all phases of studies from preclinical research to clinical trials, to postmarketing surveillance. They can be large multinational corporations to small specialty-specific groups. CROs can reduce the time it takes to bring a product to market. As clinical trials and regulations become more complex, CROs have stepped in to handle the increased workload efficiently and with enhanced performance. Some trials are multinational, and large CROs have an international presence, working with investigators and sites from around the world, each with local technical, clinical, and linguistic familiarity. This allows for rapid international recruitment of study subjects. CROs also make contracting easier for pharmaceutical companies. Their contracts set a budget, and they work within that budget to achieve results.

A pharmaceutical company or a sponsor can contract with a CRO to perform one or more of a clinical trial's duties. These duties should be spelled out in writing, in a contract. If something is not clearly written in the contract, its responsibility defaults to the sponsor. In any case, the final responsibility for the quality and integrity of the data belongs to the sponsor.

More and more research services are being outsourced to save costs and to replenish a dwindling pool of investigators (Fig. 6.4). Growth areas include outsourced services in China, India, and Eastern Europe CROs has skyrocketed. There are thousands of CROs worldwide, but consolidation is coming. Examples of dominant CROs include Quintiles, Parexel, Covance, and PPD. Examples of niche CROs in dermatology include Imavita, TKL Research, Integrium, Advanced Clinical Research Services, bioRASI, Epistem, Modoc Research Services, Pharm-Olam International, Axis Group, Clinipace, and Aptiv Solutions (Fig. 6.5).

Because productive CROs have well-established relationship with a number of sponsors, they often have access to a wide variety of clinical trials. Thus, if you as

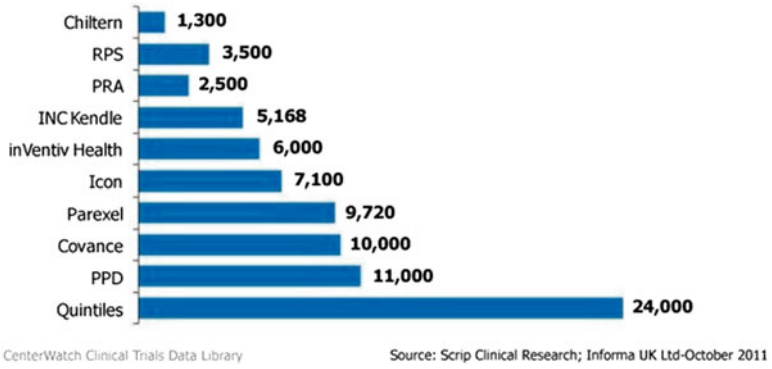


Fig. 6.5 Top CROs by worldwide employee size

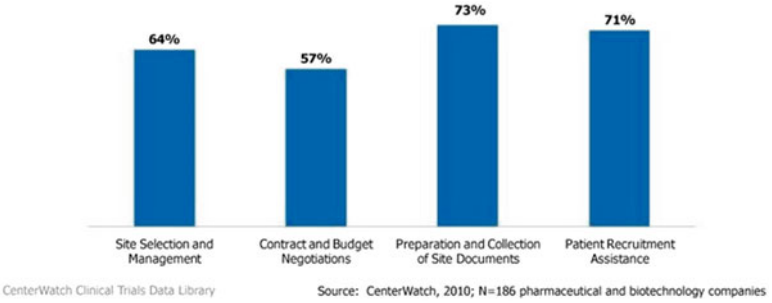


Fig. 6.6 Incidence of site management responsibilities outsourced to CROs: percent of sponsor's report "frequently/always" outsource

an investigator are trying to start studies, CROs can help get your foot in the door. If you have many studies under your belt and are a recognized leader in your field, you may be able to negotiate a better budget, work directly with the sponsor, or have sponsors seeking you for your expertise. The latter is occurring less and less, mostly because of budgetary constraints. Sponsors rarely give superstar investigators special treatment because of budgets, transparency laws, and unfair inducement laws. If you are a superstar investigator, you may have sponsors contact you for trials, and also suggest and approve you for publications or speaking engagements. These are items you can negotiate in your contract (Fig. 6.6).

6.3.4 SMO

Site Management Organizations (SMOs) differ from CROs in that they operate and manage clinical investigative sites. Whereas CROs contract with investigators and oversee the quality and integrity of clinical trials, SMOs own or manage/operate multiple research sites across USA or sometimes in several countries (Fig. 6.7).

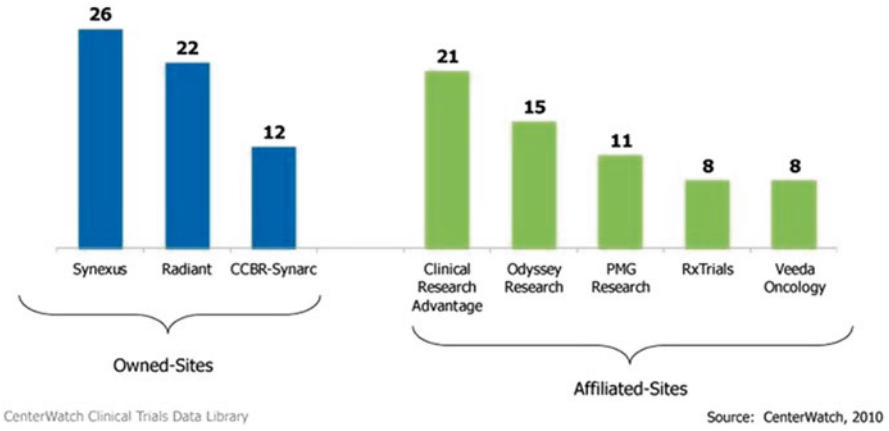


Fig. 6.7 Comparing network size (number of sites)

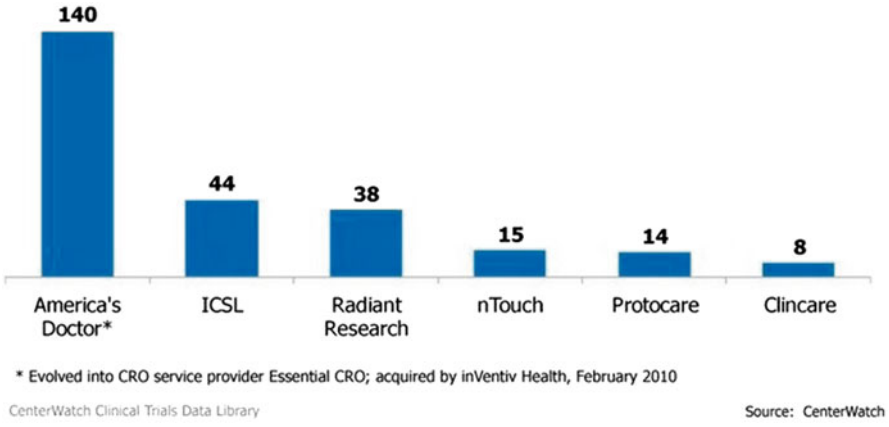


Fig. 6.8 Largest cite management organizations in 2000 (number of sites in network)

SMOs purport to reduce delays in clinical trials through outsourced research facilities operating in parallel. They handle all aspects of clinical trials including volunteer recruitment and retention. They train investigators in GCPs. They staff their sites with people who are capable of conducting complex trials and providing high quality data. They possess local knowledge and oversee local personnel who can address the requirements and regulatory hurdles of each country in which they are operating. Site management organizations serve the needs of sponsors wishing to conduct clinical trials in emerging markets, where such research is growing at a rapid rate (Fig. 6.8).

6.3.5 SMO vs. CRO

There is a great deal of pressure for speeding up clinical trials and containing costs. This has resulted in an increase in competition for investigators and sites abroad. Sometimes principal investigators are located in areas separate from sites. Data can be collected remotely and transmitted electronically. Contractors help facilitate the process. Both CROs and SMOs serve as contractors, but differ in whom they contract with, services for which they contract, and liability they assume. CROs contract with sponsors and are legally liable for their obligations. CRO is an entity that assumes, as an independent contractor with the sponsor, one or more obligations of the sponsor. For example, CROs may undertake the responsibilities of designing a protocol, selecting and monitoring investigation sites, evaluating reports, and preparing materials to be shipped and received. SMOs assume some duties of an investigational site, but regulations don't allow for transfer of clinical investigator responsibilities. Thus, a clinical investigator remains responsible for all study-related activities.

It is important to note that there is often another "contract," which is nonnegotiable, which is part of every clinical trial. And that is "Contract 1572," which uses FDA Form 1572. This is a binding contract between the investigator and the FDA. You are obligated to conduct the trial in accordance with the protocol. You can only change the protocol if the patient's safety, rights, or welfare is at stake. If changes are made, the sponsor needs to be notified. You are required to personally conduct and supervise the investigation. Make sure your list of SubIs is complete on the 1572, and that if any change, they are noted. Some sponsors will indemnify anyone on the 1572.

You are obligated to obtain informed consent. Some investigators do it personally rather than delegate it. You must report adverse events in a timely manner. Serious adverse events must be reported in 24 h. You are obligated to read and understand the investigator brochure. You're not supposed to merely use it for reference. You're required to know its contents and all about the study drug. You need to ensure that everyone understands their obligations. You must maintain accurate records. You must report all unanticipated problems promptly to the IRB. Make certain that the IRB complies with 21CFRPart 56.

6.4 Financial Disclosure

From a financial perspective, you have to make sure you and your spouse have no equity arrangement with the sponsor. It would create a conflict of interest which would raise red flags with regulatory agencies. This could lead to an audit, investigation of bias, a requirement for additional independent studies, or flat out rejection of the data obtained for FDA consideration.

Since 1999, 21 CFR 54 Financial Disclosure by Clinical Investigators has required disclosure of potential financial conflicts at the start and end of trials of

drugs, biologics, and devices. Don't balk at the disclosure. It's required by law. Your co-investigator can't balk either. It's required by law. Disclosure applies to spouse and dependents for up to a year after the close of a study. A study may close at your site, but not for the entire trial. You have to date your final disclosure to the time period after the end of the trial, or according to the sponsor's instructions. By signing form FDA 3454, you, as the investigator, certify that:

- Everyone on item 6 of HCFA 1572 has no financial arrangement which would affect the outcome of the study.
- You do not have a significant (>$50K) equity in the sponsor.
- You do not have a proprietary interest in a related patent, trademark, copyright, or license.
- You have not received more than $25K for consulting, speaking, equipment, new construction, or other compensation. Nor has the investigator's site.

Applicable conflicts must be disclosed, on a different form (FDA 3455). FDA regulations governing disclosures are updated every April and October at www.FDA.gov under 21 CFR part 312. Financial disclosure is required for all studies in a US IND application, even if conducted abroad. In 2008, Norman Goldfarb discovered the following disclosure deficiencies:

- <2 % of investigators disclosed financial conflicts of interest.
- 26 (53 %) of NDAs disclose COIs.
- Most COIs come from only a few sites (five NDAs accounted for 67 % of COIs, one NDA accounts for 22 % of COIs).

However, failure to disclose COI can lead to an FDA audit, and to the exclusion of any data you gathered data from analysis. Be sure to be aware of and periodically update your financial conflicts of interest, as some of them apply for a time period after the conclusion of a study.

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Chapter 7
Legal Issues Related to Human Subjects for Research

Margarita S. Lolis and David J. Goldberg

7.1 Introduction

The conduct of medical research that involves human subjects has many ethical and legal implications. Great strides in protecting the welfare and safety of research participants have been made in the past 40 years due to a series of unethical events. This chapter will focus on the history and evolution of the ethical and legal measures that have been implemented to safely conduct human research.

7.2 History

The most infamous medical research study in the history of the USA is arguably the Tuskegee syphilis experiment. From 1932 to 1972, the US Public Health Service conducted a prospective study on 399 African-American males entitled, "The Tuskegee Study of Untreated Syphilis in the Negro Male." Several breaches in ethical standards occurred. Subjects did not give informed consent, were not informed of their diagnosis, believed they were receiving free medical care, and did not receive appropriate treatment once it was discovered [1]. The study was finally terminated in November 1972 once the ethical shortcomings were made public by a

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Table 7.1 Timeline of laws related to the protection of human subjects

BC	*Hippocratic Oath*
	Code of professional ethics
1938	*Food and Drug Act*
	Requires drugs be proven safe before marketing
1947	*Nuremberg Code*
	Informed consent required for human studies
1964	*Helsinki Declaration signed by the USA*
1966	*US Surgeon General Policy Statement*
	All human subject research requires review. Origin of IRB
1974	*National Research Act*
	All federal funded research to be reviewed by IRB
1979	*Belmont Report*
1980–1983	*President's Commission*
	Recommended all federal agencies adopt regulations of HHS
1991	*Common Rule*

whistle-blower [1]. This led to many changes in laws and regulations involving human subjects involved in research studies.

In the aftermath of the Tuskegee syphilis experiment, the 1974 Research Act was formed, which led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Table 7.1). The purpose of this commission was to identify and develop basic ethical principles related to the conduction of research in human subjects and form guidelines based on these principles that should be universally applied. The Commission published a report in 1978, known as the Belmont Report, which summarized these ethical guidelines. Three core principles were delineated in the report, which included respect for persons, beneficence, and justice. The primary applications of these guidelines included informed consent, assessment of risks and benefits, and selection of subjects. Currently, the Belmont Report forms the basis of regulations enforced by the Department of Health and Human Services (HHS) and as a reference for institutional review boards (IRB) [1–6].

In 1981, the HHS and Food and Drug Administration (FDA) began making amendments to the Belmont Report. At that time, different institutions and agencies have various policies regarding the conduction of human research studies. In 1991, the "Common Rule" (Code of Federal Regulations Title 45, Part 46) was enacted to create a universal policy to be followed by all agencies except the FDA [1, 5, 6].

HHS has since made many further revisions, amendments, and additional regulations, with additional protections for special subjects, including pregnant women, fetuses, neonates, children, and prisoners.

7.3 Ethical Issues Surrounding Human Subjects

Several ethical issues arise when designing and implementing a research study in human subjects, which include (1) safety, (2) voluntary participation, (3) confidentiality, and (4) adverse events. First and foremost is the safety of the research participant. For any study, the potential benefits must outweigh the risks, and continual monitoring of the safety of the project should occur throughout the duration of the study. Willingness to participate in the study is another ethical issue. Individuals must provide written, and in some cases, oral consent after appropriate discussion of risks and benefits, and the opportunity to review questions and concerns. Confidentiality and patient privacy should always be addressed. Protection of patient information must be considered and outlined. The tracking and management of adverse events should be clearly planned, as well as compensation related to the event [7].

7.4 Basic Ethical Principles of Research Involving Human Subjects

The ethical standards that govern research in human subjects are based on the principles of autonomy, beneficence, and justice. The concept of autonomy is based on respect for individuals. Each subject must be treated as an individual who is capable of making an informed decision. The researcher must ensure that the participant has had full disclosure of all the risks and benefits of the study, the nature of the study, the duration of the study, as well as alternatives. Researchers must be truthful. Included in this concept is that individuals with decreased autonomy are entitled to special protection. Examples include children, neonates, prisoners, and additional regulations have been implemented to offer additional protection to these individuals. The informed consent is the best application of this principle. Subjects enrolled in research studies must be informed of the risks and benefits and must consent to treatment.

Beneficence is based on the concept of not providing harm to individuals. The intent of the study should be to maximize the possible benefits for the participant, and minimize the possible harm or risk from the research. The third principle, justice, ensures that the benefits and burdens of the study are distributed evenly and fairly, so that no group of individuals is exploited [1, 2, 5, 8].

7.5 Informed Consent

The informed consent is a vital part of any research study involving human subjects (Table 7.2). As previously mentioned, the informed consent is based on the principle of autonomy, or recognizing that each individual has the capacity to make an informed decision. The informed consent must have certain components to render it ethical and valid.

Table 7.2 Key components of informed consent

Statement that the study involves research
Research is described
Description of risks
Description of benefits
Disclosure of alternatives
Confidentiality
If more than minimal risk, compensation and/or medical treatment
Participation is voluntary
Whom to contact
Unforeseeable risks
Early termination
Additional costs to subjects
Consequences of a subject's decision to withdraw from study participation
Disclosing new findings which may impact a subject's willingness to continue participation
Number of subjects involved

First, there must be disclosure. The nature and purpose of the study, the procedures used, the expected benefits to the individual and society, the potential risks of the research, and alternatives to participation in the study must be discussed. Furthermore, there must be privacy and anonymity of the participants and information of what precautions will be taken to ensure this. Also included in the informed consent should be information of compensation and medical treatment are available in the case of a research-related injury.

Understanding is another component of the informed consent. The participant must demonstrate understanding, have the opportunity to raise questions and concerns and have them addressed.

Participation in the research study must be voluntary, free of coercion or promises. Subjects should be able to withdraw from the study at any point.

Participants must be deemed competent to provide consent. Subjects with mental illnesses, cognitive deficiency, or disease may have a designated surrogate provide consent if it is the best interest of the patient.

Lastly, the human subject must authorize his/her involvement in the research study with written consent. Informed consent is required by the law [7–9].

7.6 Current Regulations in the USA

Research involving human subjects is controlled by two federal agencies, the HHS and the Office for Human Research Protections (OHRP). The OHRP is a federal department designed to ensure the protection, welfare, and safety of human subjects involved in research conducted or supported by the HHS. It does so by providing

guidance, maintaining regulatory oversight, ensuring institutions comply with the Common Law, and developing educational programs on ethical issues in biomedical research. The federal regulations adapted by the HHS are now followed by most US health care institutions conducting research and are generally applied to all research protocols. Research that involves the testing of investigational drugs or medical devices is regulated by the federal Food and Drug Administration (FDA) [3, 4].

Generally, research on human subjects must be reviewed and initially approved, overseen, and annually reapproved by an IRB, which is recognized by the federal Office of Human Research Protections (OHRP), a division of the HHS.

Inset 7.1

Nanotechnology

Rules and regulations are evolving to keep pace with developments in technology, such as recombinant DNA technology, and nanotechnology. Nanotechnology has experienced an explosion in development over the past two decades in consumer products and in medicine. The greatest number of new patents incorporating nanotechnology over the past decade have targeted the skin in products ranging from sunscreens, to topical delivery and systemic medications, to diagnostic devices. One of the earliest nanoparticulate drugs to be approved was liposomal doxorubicin, which is used for the treatment of Kaposi sarcoma. Nanotechnology is the study of particles 100 nm or smaller in size. The vast majority of biologically important processes (nucleic acid replication, enzyme activity, cell membrane interactions, etc.) occur in the nanometer size range. Matter is known to behave differently at the nanoscale. Drug and device developers are capitalizing on these new properties of matter to create novel tools for the maintenance of skin health, and the diagnosis, and management of skin disease. There have been concerns expressed about the potential toxicity of nanomaterials, and a call for the FDA to offer guidelines for the public and industry in this arena. In 2013, the FDA, issued a special policy on nanomaterials for public comment:

FDA will continue to regulate nanotechnology products under its existing statutory authorities, in accordance with the specific legal standards applicable to each type of product under its jurisdiction. FDA intends to ensure transparent and predictable regulatory pathways grounded in the best available science.

- One size does not fit all. We intend our regulatory approach to be adaptive and flexible. It is necessary for technical assessments to be product-specific, taking into account the effects of nanomaterials in the particular biological and mechanical context of each product and its intended use.

- Particular approaches for each product area will vary according to the statutory authorities. The scope and issues covered in the two draft guidance documents released today—one for foods and one for cosmetics—reflect this approach.
- FDA's regulatory policy approach is consistent with relevant overarching U.S. government policy principles, and supports innovation under appropriate oversight.

Industry remains responsible for ensuring that its products meet all applicable legal requirements, including standards for safety—regardless of the emerging nature of a technology involved in the manufacturing a product. *FDA encourages industry to consult early with the agency to address any questions related to the safety, effectiveness, or other attributes of products that contain nanomaterials, or about the regulatory status of such products.*

The FDA is examining novel nanotechnology based applications on a case-by-case basis and urging close consultation and guidance at the early stages of development in order to maximize patient safety and minimize unnecessary or inappropriate or inadequate studies.

7.7 The Institutional Review Board

The purpose of the institutional review board (IRB) is to ensure the protection and safety of human subjects used in research. It does so by independently reviewing research proposal and determining whether they fulfill ethical standards. All institutions that conduct federally funded research projects must provide an "assurance" that outlines the institutions principles for protecting human subjects used in research. Under the Common Rule, this assurance is executed by designating IRBs [1] (Table 7.3).

In accordance with federal policies, an IRB must be composed of at least five individuals: a chairperson, a scientific member, a nonscientific member, a layperson not affiliated with the institution, and a practitioner. This committee is responsible for reviewed research proposals. The federal law has established three types of review: exempt, expedited, and full. Studies that are exempt from IRB review are those that present minimal risk to the human subjects. Research studies that undergo expedited review do not undergo review by a full committee, but rather the IRB chairperson. These studies generally involves slightly more than "minimal risk" to the subjects. A minimal risk study is defined as one in which the risk of harm is no greater than daily life experiences. All other research studies are required to undergo a full review [1].

Certain requirements are mandatory for a research study to gain approval by the IRB. The risk must be minimized by a thorough and reasonable study design. The risks must be reasonable and balanced by the possible benefit of the study.

Table 7.3 Criteria for IRB approval

Risks are minimized
Risks are reasonable compared to expected benefits
Subject selection is equitable
Informed consent is obtained and documented
Research proposal provides plan for monitoring data collected
Research proposal protects privacy of subjects and maintains confidentiality
Additional safeguards are implemented to protect right of subjects who are vulnerable to coercion or undue influence

Subjects should represent the general population and ideally not draw from a vulnerable group of individuals. If this does occur and there is risk of coercion, then a protocol of how extra protection of subjects must be delineated. Other requirements include explanation of data monitoring, maintaining patient confidentiality, and obtained informed consent. Last, the IRB review is ongoing, and continual [1, 4].

7.8 Conclusion

Great progress has been made in ensuring the protection and welfare of human subjects used in research projects. Though federal laws have been enacted and internal safeguards have been enforced to ensure participant safety and awareness, ethical issues still remain. One of the more pressing issues is the role and appropriateness of incentives in research involving human subjects. Incentives, typically financial, may be viewed by some as a form of coercion or influence. Though usually harmless, one can imagine certain situations where ethical questions arise, particularly when the risks are substantial. Another pressing concern is that most of the implemented safeguards are only in place for research projects receiving federal funding, and dependent on the voluntary cooperation of research investigators, institutions, companies, and professional societies [2]. Despite these challenges and issues, the government, private and public institutions, and many independent researchers have worked together to create solid and ethical research studies to improve healthcare and ultimately benefit mankind.

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Chapter 8
Ethics

Kevin Yang, Anil Kurian, and Benjamin Barankin

8.1 Introduction

"First, do no harm"—an apt description of one of medicine's central tenets. So too in dermatology does this platitude apply. But in addition to simply doing no physical harm, the field of dermatology follows principles that extend beyond just the physical health of patients.

Skincare is a multi-billion dollar industry. Not surprisingly, given the societal impact that the skin has, ethical issues commonly arise within dermatology research. For instance, private industries often subsidize clinical trials or hire independent research firms to help expedite the process. As well, it is not unusual for private dermatology offices and even university institutions to have a share in the skin care industry [1]. Clinicians involved in dermatology research therefore need to be particularly cognizant of ethical considerations. To participate in dermatology clinical trials necessitates understanding the core principles of medical ethics, and together they represent one of the core competencies mandated by the Royal College of Physicians and Surgeons [2]. Several papers have outlined how dermatology residency programs are currently teaching their residents about this important topic [3, 4]. However, according to a survey conducted across Canadian dermatology program, a large percentage of trainees felt that teaching of ethics and professionalism was inadequate [2]. This again underlines the importance of learning the ethical groundwork.

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In this chapter, we will lay the foundation of medical ethics using pertinent dermatology examples. The sections in this chapter are as follows: codes and guidelines, autonomy, beneficence, non-maleficence, and justice. These ethical principles are relatable to both patient care as well as research.

8.2 Codes of Ethics

Many ethical codes are already in place, and being familiar with what already exists locally is important. The World Medical Association, American Medical Association, and Canadian Medical association each have their own codes that share many of the same principles. An ethical code is a document erected by an organization that outlines its beliefs and values. Ethical codes act as a guide to help physicians and researchers resolve ethical problems. Admittedly these principles have their own limitation—they may not be applicable to all situations, and may sometimes even conflict with each other. That said, ethical codes provide a good framework for resolving ethical dilemmas.

Inset 8.1
During World War II and after, pharmaceutical research became a large enterprise sponsored by government and industry. Large numbers of trials were conducted on captive volunteers, such as military personnel, prisoners, and institutionalized individuals (mentally ill, orphans, physically handicapped). In fact, many large academic medical centers and pharmaceutical companies had their research sites located near institutions, sometimes just across the street. Mishaps, tragedies, and cases of wartime and peacetime abuse led to ethics convocations and the promulgation of laws protecting human subjects and empowering agencies such as the FDA to develop guidelines to ensure the safety and ethical conduct of clinical research involving human subjects.

One of the pioneering ethical codes was the Nuremberg Code, a set of research principles established in 1949 as a result of the Nuremberg Trials for the war crimes committed by the Nazis [5]. The physicians and scientists were on trial for the grotesque experimentation that took place in concentration camps. The Nuremberg Code consists of ten arguments outlining how humans should be treated in research. Although the document was established over half a decade ago, its themes still resonate to this day.

Subsequent to the Nuremberg Code, the Declaration of Helsinki was created in 1964 by the World Medical Association and the Belmont Report in 1979 by the

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. These subsequent guidelines summarized the main ethical principles when conducting biomedical research on human subjects, and touches upon such topics as: establishing a boundary between practice and research, ethical pillars, informed consent, risk versus benefits, and subject selection (Table 8.1).

Inset 8.2

FDA

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC): The IRB/IEC oversees ethical, regulatory, and safety aspects of the trial at an individual study site, and decides what constitutes informed consent. IRB/IECs can be local, or institutional, or national. No IRB/IEC is without conflict of interest. Local and institutional IRB/IECs can have conflicts of interest related to promoting the prestige of the institutions or some of their faculty. Alternatively, they may meet less often and move slower than professional IRB/IECs because of their all-volunteer staff. Professional IRB/IECs funded by sponsors can have conflicts of interest because a competitive environment requires speedy approval. IRBs must have a composition which maximizes its diversity and its emphasis on the protection of the health and safety of human subjects. They must have a minimum of five members of diverse backgrounds and genders, and must include one lay-person and one person who is not affiliated with the institution requesting approval. IRBs may not reject or request modification of a protocol, but they have been known to reject an individual investigator or site.
- Food and Drug Administration (FDA): The FDA assures regulatory oversight for the pharmaceutical industry, and monitors for the public the quality and safety of all drugs and devices in this country. The FDA is not without bias, as its approval process is almost entirely funded by industry. Furthermore, congressional politics occasionally intervene in the selection of FDA leadership, priorities of regulation, and appropriations for its mission.

The FDA budget has a conflict of interest. Nearly half of its support (42 % in 2006) comes from user fees, paid by the pharmaceutical industry This money, from industry, is not merely handed over to the FDA carte blanche. Industry has detailed input into how the money is spent. FDA recently approved an unsafe knee device Menaflex, after the FDA received “extreme” “unusual” and persistent pressure from four Democratic legislators from New Jersey.

Table 8.1 Summary and comparison of ethical codes [6, 7]

Nuremberg Code (adopted in 1949)	Declaration of Helsinki (adopted in 1964)
Voluntary consent	Informed consent
Beneficial to society	Purpose of research is to better our understanding of diseases
Built on animal studies/previous knowledge	Conform to prior scientific principles
Minimize physical and mental harm	Physicians should act in best interest of patients
Deny study if there is a suspicion that death or severe mortality may occur	Duty to protect research subjects and maintain ethical standards
Minimize risks	The goals of a research study itself should never take precedence over the wellbeing of the research subjects
Experiments should be conducted by scientists and professionals	Experiments should be conducted only by those with adequate ethics and scientific training
Subjects' right to leave the study at any point	Compensate subjects who are harmed
Lead investigators' duty to stop a study if continuing it will lead to disproportionate harm	Duty to protect health, rights, privacy, confidentiality, and dignity of research subjects
Proper facilities and operations to minimize harm	Protect vulnerable groups
	Approval by an ethics committee

8.3 Ethical Principles

Our discussion begins by answering the question: "What are the basic ethical principles?" These four principles, now mainstream, were first championed by Beauchamp and Childress in their book *Principles of Biomedical Ethics* [8]. They proposed an analytical framework composed of: (1) autonomy, (2) beneficence, (3) non-maleficence, and (4) justice. Autonomy refers to the rights that a competent and mature patient has in making decisions regarding their health care. Beneficence outlines how clinicians and researchers should make decisions that maximize the benefit for a patient, specific for their situation. Non-maleficence is the idea that harm should be avoided whenever possible and risks reduced at all costs. Justice refers to the equal distribution of health resources, void of discrimination. We will now go into a detailed discussion of each ethical pillar.

Inset 8.3
In the preclinical phase, animals must be treated humanely under the supervision of an Animal Care and Use Committee (ACUC) following Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) guidelines. Trials should use as few animals as feasible, minimize the intensity and duration of pain or stress to the animals, and substitute other materials such as cell lines or lower species whenever possible.

8.4 Autonomy

Autonomy directly opposes the obsolete perspective that the physician is the ultimate authority. It is a concept that enables the patient to share, alongside medical providers, in his or her own care. Autonomy is particularly important to participants in research trials because their enrolment is not only optional, but they may actually receive little benefit from enrolling. And because physicians are in a fiduciary relationship with their patients, they are susceptible to intimidation and coercion. Autonomy therefore stresses the importance of protecting patients' personal and best interests. Allowing patients the opportunity to drop out of a study at any point in a study is one of many ways to protect patient autonomy.

Allen Hornblum's book *Acres of Skin* [9] showcases how one American dermatologist exploited prison inmates, ultimately compromising patient autonomy. The book, based on real government documents, inquiries, and interviews, reveals some concerning research that took place in Philadelphia's Holmesburg Prison [9]. The lead investigator behind the experiments, Dr. Albert Kligman, was a prolific dermatologist and researcher renowned for developing Retin-A® and the concept of cosmeceuticals, among many other discoveries. He bridged the gap and blurred the lines between cosmetics and medicine. Funded in part by the University of Pennsylvania, prisoners were paid for each experiment they enrolled in. The amount of money they received for experiments ranged from $10 to $300 per experiment [9] and was disproportionately higher than the money they would receive from more laborious jobs in prison. The lure of money was enough for prisoners to undergo sometimes uncomfortable testing, and it was thought that the vast majority of these prisoners decided to enroll. Many of them were fearful of the experiments, but carried through with it regardless.

Superficially speaking, one could argue that the prisoners did have some patient autonomy. They did have a choice regarding whether to enroll in the research program, and what type of experiment they preferred. Still, this argument is inherently flawed because prisoners are in a vulnerable position in which their autonomy and personal liberties are already restricted. Monetary incentives were used to take advantage of their position, and represent a means of stripping away their autonomy. The prisoners were not given a large amount of money; but, given their bleak environment, they were compelled to carry through with it even if they were fearful of the experiments. With very few other options, enrolling in these experiments was a way for the inmates in Holmesburg prison to make a moderate income compared to working elsewhere. Owing to this incident, hundreds of Philadelphia inmates filed a lawsuit against the researchers, industries, and institutions involved [10]. Unfortunately, the lawsuit was unsuccessful because it took place beyond the statute of limitations [11]. University of Pennsylvania later released an apology for the Holmesburg experimentation [12], which ended as a consequence of regulations put in place that prevented coercion and restricted the use of prisoners as test subjects. The National Research Act of 1974 was established to restrict the use of prisoners as test subjects, and to put in place ethical review boards within research institutions [12]. These regulations were enacted in part as a consequence of the Tuskegee

Syphillis study and later became the Belmont Report. We will discuss the Tuskegee study later on in this chapter.

What would have been the ethical thing to do? Admittedly, there are advantages to using prisoners as research subjects, both from a scientific perspective as well as from the prisoner's point of view. Inmates are human beings like anyone else, and will have medical conditions that would benefit from new drug trials. Certain diseases are more prevalent in prison systems, and it would be beneficial for researchers to have access to this environment so as to learn more about how to prevent disease in prisons. Inmates may also gain intrinsic reward by gaining a sense that they are helping the greater community by volunteering [13]. They also benefit from the attention given to them by "outsiders", which instills in them a sense of societal importance. In light of all of this, physicians should be extra cautious, not only to respect autonomy, but to protect it among an otherwise compromised population. The higher prevalence of mental illness adds to the need to protect autonomy for those that may lack capacity.

One review article outlines several recommendations that address the use of prisoners as research subjects [13]. First, material incentives such as disproportionate sums of money or food should not be used. Payment, if any at all, should be proportional to wages earned in other areas of the prison. Doing so will allow inmates the option to pursue "equivalent" opportunities rather than become lured into something they do not want to do for external gains. Second, only therapeutic research should be performed. Non-therapeutic studies garner no benefit for participants, and have low yield in terms of the benefit-risk ratio. They mainly cause unnecessary risk exposure. In the case of Dr. Kligman's experiments, many of the studies were non-therapeutic and driven by industry, money, or curiosity. The final recommendation is that external reviewers should be employed to provide an unbiased authority over the experiments and institutions involved in the research.

Clearly there needs to be a careful balance between promoting useful research and protecting prisoners. Our viewpoint on research with prisoners is in line with guidelines outlined in the Belmont Report. We feel that research involving prisoners is ethical on the assumption that there be [14]:

1. Justice: prisoners should be given opportunities for getting involved in research instead of being deprived of this.
2. Respect for persons: prisoners are in a vulnerable position and can be easily coerced or manipulated given their conditions. Scientists need to ensure that prisoners are free of any elusive coercion.
3. Fair selection of subjects: prisoners should not be preferentially chosen as test subjects for studies that have more "risk".
4. Strong therapeutic component: research with inmates should have a therapeutic component to avoid unnecessary harm to an already vulnerable population.
5. A national research database to help regulate what studies have already been undertaken and to better facilitate/implement future studies [1].
6. Privacy: it is inherently difficult to maintain privacy and confidentiality in the overcrowded prison system. However, measures should be taken to maintain the respect and dignity of prisoner research subjects [1].

8.5 Beneficence

The line "I will come for the benefit of the sick" from the Hippocratic Oath is a fitting reminder for physicians to always try and help others. Beneficence pertains to the idea that physicians should act to help others. They should promote the best treatment for that patient and minimize harm as much as possible. The Belmont Report suggests two general rules with beneficence: (1) do not harm, and (2) maximize benefit while minimizing harm [14]. Especially true when conducting clinical trials, scientists should not put their research subjects in harm's way and should act in the best interest of their patients (Table 8.2).

A dilemma with randomized control trials is the paradox between beneficence and randomization. In an ideal scientific setting, researchers should genuinely have no idea about what treatment is the more effective one. However, most physicians do have an inclination about which treatment might work better [15]. Or, they may gain insight as the study progresses based on preliminary data. Given these assumptions, how can a physician continue to randomize patients if they already have an idea about what treatment is more effective? One explanation that some have proposed is the notion of "community equipoise" [16] outlined by Gifford. The idea is that an individual researcher may have formed an opinion about the treatments, but because there is uncertainty among the greater scientific community, the researcher can continue randomizing patients ethically. Another way around this dilemma is to ensure that preliminary results are not disclosed to the physicians involved. Doing so will prevent them from having a preference for treatment. That said, one could argue that the physician is not providing the best care for the patient if he knows that there is data out there which may help him provide better care. Gifford's paper argues that defending randomization using "community equipoise" is insufficient. In order to justify randomized control trials, the therapeutic duty needs to be relaxed and informed consent more comprehensive.

Inset 8.4
Issues such as ownership of tissue and genetic material are being debated in the courts. The famous case of Henrietta Lacks and cell culture lines derived from her tissues without consent have been well-documented abuses. More recently, participants in clinical trials have contested patents derived from their tissues and genetic materials. Courts have generally sided with companies and patent holders, denying research study volunteers ownership rights or royalties from any intellectual property derived from their participation. In 2013, the US Supreme Court, in an apparent reversal of judicial precedent, raised the bar on patenting of genes and genetic material, making its patenting more difficult for manufacturers.

Table 8.2 Principles of beneficence

Principle	Example of adherence	Example of violation
Do not harm	Stopping a clinical trial if preliminary results show that the drug is causing serious and severe side effects	Carrying through with a clinical trial despite prior knowledge of serious and adverse effects of a drug
Maximize benefit while minimizing harm	Offering the control group the opportunity for treatment if preliminary analysis shows promising results with the experimental treatment	Carrying through with a clinical trial and withholding treatment despite prior knowledge that the condition is treatable

Another dilemma faced with clinical trials is whether or not the use of placebos is ethical. Placebo controls are attractive because they strengthen statistical significance and establish a baseline as to whether the drug is better than no treatment. But their use remains controversial. Hothman suggests that placebos deny patients from receiving the best available treatment. Additionally, he argues that the informed consent process should not allow patients to agree to a lesser treatment. More ethically sound are clinical trials that compare an experimental group with an established drug. This approach is less controversial because, at the very least, the participants are receiving treatment, which may sometimes be the gold standard, with proven benefit.

Stopping a clinical trial early because of demonstrated benefit is becoming an increasingly common practice [17]. The idea behind stopping a clinical trial early for benefit is to allow all participants the treatment when preliminary analysis has shown significant benefit over the control group. The rules for stopping a clinical trial are often elusive and many studies do not adequately explain their rationale for stopping the clinical trial. Clearly, though, scientists are increasingly cognizant of the concept of beneficence taking priority over scientific pursuit. A truncated clinical trial provides only a snapshot of the overall effectiveness of a treatment, and thus may produce exaggerated results.

Upholding beneficence is also problematic with dermatology practices. Whenever a source of conflict of interest arises, there is a likelihood that beneficence will be undermined. For instance, there is debate as to whether selling over-the-counter skin care products in office is ethical [18]. This is a common practice among dermatologists who argue that doing so is both convenient for patients and provides them with comprehensive care. Opponents are not convinced that the products being sold are always in the patient's best interest. The products endorsed in office may not necessarily have evidence behind its claims, and because they are endorsed within a medical setting, patient can easily be misled. The American Medical Association acknowledges that selling health-related products in office may "undermine the primary obligation of physicians to serve the interests of their patients before their own" [19]. They do not openly endorse nor refute this practice, but do provide certain recommendations. They suggest that the products offered have strong, peer-reviewed, scientific evidence behind them and that any financial disclosures be made very apparent. The American Academy of Dermatology also released guide-

lines for in-office dispensing [20]. They recommend that in-office dispensing can ethically take place if in the best interest of the patient, but with several exceptions:

1. The physician's financial interests take precedence over patient well being
2. There is subtle coercion to buy products
3. Not listing the ingredients in a privately labelled product
4. Not informing patients that the product may be more readily accessible at local pharmacies
5. Claiming exclusive selling rights of a product when that is not true
6. Selling products with unsupported claims of benefit
7. Barring patients the opportunity to refill medications unless they be bought from the office
8. Excessively marking up the price of products

Conflicts of interest are also apparent at the level of research institutions [1, 21, 22]. There have been several instances where research-heavy universities have been faulted for accepting sponsorship from non-pharmaceutical industries in exchange for either naming rights or to have their endorsement on products. When Johns Hopkins University acted as a consultant for Klinger Advanced Aesthetics, they initially accepted equity as well as a board position in the company to allow their name and logo to be used on products [23]. Some people were surprised that a well-respected university would agree to endorse a product that they were testing—an example of both conflict of interest as well as disregard of beneficence. Consumers that encounter a product with a Johns Hopkins symbol may be misled into choosing their product over others even if it is not any better than other products or in their best interest. Soon after this incident was made public, Johns Hopkins released a statement announcing that they would revoke any equity and board positions and would discontinue all endorsements on products. Other controversial events include Cornell's affiliation with Clinique [22], and physicians offering free treatments to journalists in exchange for articles to be written up about them [24]. In all of these instances, the patient's best interest is second to the personal interests of the physician or institution. One study found that many reputable universities lack strong enough policies to prevent personal investment into companies that they do research with [1]. The article recommends that researchers should not be allowed to hold stocks, stock options, or sit in any of the company's positions of power.

8.6 Non-maleficence

Simply put, non-maleficence translates to doing no harm. This task is a seemingly impossible one, because any intervention has its own risks. That said, physicians should strive to minimize harm at all costs, and to adjudicate the risk–benefit ratio to determine whether it is in the patient's best interest to be exposed to possible harm. Non-maleficence also refers to avoiding harm by withholding intervention if

the risk of harm is too high. Non-maleficence and beneficence can sometimes come into conflict. If a physician's main goal is to improve the patient's survival (thus exerting beneficence), he or she is also exposing the patient to increased risk of harm (maleficence).

Dermatology clinical trials sometimes overlook the importance of non-maleficence. Using again the example of the experiments at Holmesburg Prison, many of the inmates suffered pain or scarring from the experiments. The risk of injury was therefore high, while the benefits would be minimal if the experiment was non-therapeutic. Clearly then the risk–benefit ratio was not properly adjudicated.

In addition, a study that analyzed 58 negative-result clinical trials from *British Dermatology Journal* [25] found that the vast majority of these studies were found to have too small of a sample size and had a high probability of incorrectly missing a treatment difference. In other words, many of the studies were performed without producing meaningful results, and participants were exposed to unnecessary risks. The study also took issue with how most studies did not include confidence intervals, and some studies even had data that was incorrectly interpreted. Part of what makes a clinical trial ethical is that the knowledge gained from the study is worthwhile and will benefit society [26]. Underpowered studies often serve little purpose and only expose volunteers to unnecessary risks [27]. They result in wide confidence intervals containing both positive and negative results. Opponents could argue that small studies can eventually be combined together via a meta-analysis to estimate treatment effect, or that small studies are ethical if the disease being studied is rare. As well, small studies may arguably be more acceptable if it is an early phase look at a drug.

Inset 8.5

Research is also in an era of big data. Projects such as the Cancer Genome Project are gathering enormous quantities of data on subjects, including personal information, demographic information, detailed case histories with thousands or millions of data points, and laboratory data including longitudinal and prospective gene sequencing data. Subjects are located in the United States and the rest of the world. These massive archives of data are being made analyzed with powerful computers such as IBM's Watson to look for patterns that may not be obvious to human researchers. They are also being filtered through online medical decision support tools. The depth detail of the data, combined with online accessibility, albeit through secure channels, make the risk of data breach a real concern. The privacy of human subjects is harder to protect in the electronic era, and additional rules have been developed to ensure privacy and anonymity. Privacy is pitted against public interest in community studies and large population studies which try to electronically extract useful clinical and genetic data from hundreds, thousands, and millions of individuals. Data mining of this type requires unique identifiers to be missing.

In order to address the problem of underpowered studies, some suggest that an ethics committee should first review these studies beforehand to ensure they are ethically sound [25]. The purpose of an ethics committee is to highlight and address any potential ethical dilemmas. The American Academy of Dermatology has an overarching Ethics Committee that reviews complaints and establishes guidelines, but does not reinforce rules [28]. Instead of acting as a disciplinary body, the committee formally set out The Code of Medical Ethics in 2005 which decisively outlines the ethical responsibilities and standards of dermatologists.

Inset 8.6
Use of technology to communicate with patients
Technology to maintain compliance or adherence
Privacy

Text-message reminders to improve sunscreen use: a randomized, controlled trial using electronic monitoring. Armstrong AW, Watson AJ, Makredes M, Frangos JE, Kimball AB, Kvedar JC. Arch Dermatol. 2009;145(11):1230-6.

In this study in the greater Boston metropolitan area, 70 volunteers 18 years and older with cell phones and texting ability were divided into two randomized groups. One group received daily text reminders to wear sunscreen. The other did not over 6 weeks. A hook had the daily weather, and a prompt had a sunscreen wearing reminder. Mean adherence was 30 % in the no text group and 56 % in the text group. Eighty-nine percent said they would recommend text reminders to their peers. The study demonstrated increased adherence with mobile phone reminders. The study did not examine privacy information, such as metadata embedded in the mobile phone and transmitted to carriers. Future studies using this technology—especially those of a more personal or sensitive nature, such as studies of human papillomavirus therapy or herpes simplex virus therapy—may require anonymization or permanent erasure of all identifiable metadata.

8.7 Justice

Justice refers to the equal distribution and fair access of medical resources. This means that patients who are in comparable situations from a medical standpoint should not be discriminated against based on factors that do not impact their condition (e.g. wealth, race, religion). A historical example commonly used to showcase injustice is that of the Tuskegee syphilis experiment [29] beginning in 1932. The study took place among lower socioeconomic African Americans in Alabama. They were kept in the dark about their medical conditions and never offered treatment. Despite penicillin becoming the standard of therapy for syphilis in 1947,

researchers continued to withhold this information from those enrolled in the study. Consequently, none of the research participants were treated properly and many of them even died from syphilis. The American government later released an apology and acknowledged that the study, in which researchers prevented the black study participants from receiving proper treatment, was clearly racist. The Tuskegee syphilis experiment has become a frequently cited example of unethical experimentation, violating all ethical boundaries. Autonomy was not withheld because researchers neglected the fact that they were dealing with a vulnerable population easily enticed to enroll in the study in exchange for "free medical services". Informed consent was not properly obtained because the participants were unaware of the purpose of the study or their diagnosis. Beneficence and non-maleficence were not upheld: despite researchers knowing that there was a treatment available, they did not act in the best interest of their patients. Withholding treatment led to harm and even death. Justice was not exercised because the study participants were chosen for their lower socioeconomic status and not given equal opportunity for treatment.

More subtle, but equally important, examples of injustice can be seen within dermatology. Many skin conditions are exquisitely rare while others are very common. This disparity in prevalence poses a significant problem for fair distribution of resources in research and development [30]. Because pharmaceutical companies typically pay more attention to therapies addressing prevalent conditions, less attention is paid to rare conditions with a small market. Pharmaceutical companies are more inclined to invest in developing therapies that results in more financial returns versus a therapy with a very small market. To address increasing public pressure and lobbying from the National Organization of Rare Disorders, the Orphan Drug Act (ODA) was enacted in 1983 [31]. The ODA promotes research and development of treatment for rare diseases by providing pharmaceutical companies monetary incentives such as market exclusivity, tax credits, grants, fee waivers, and more. A disease is considered rare if its prevalence is fewer than 200,000 US citizens. The ODA has generally been regarded as successful and resulted in an enormous increase in the number of drugs for rare diseases [31]. One commonly cited example was the development of several effective drugs, which was a direct result of the ODA, for treating cystic fibrosis (Cheung). Following the ODA, the Rare Disease Act of 2002 was adopted to formally establish the Office of Rare Diseases at the National Institute of Health. This further increased funding for addressing rare conditions [32].

In addition to unequal distribution of resources among different diseases, there is also an unfair distribution of resources among those being treated for the same disease [33]. In conditions like psoriasis, there is a wide range of treatments with varying costs. By far the most expensive treatments are the biologics. Pharmaceutical companies charge a large amount of money in order to recuperate the costs of their research and development. But if these medications have been shown to be more efficacious and tolerable than existing medications, then is it in the best interest of all patients to receive biologics? How do we maintain fair distribution for a drug that is exorbitant in cost? Dermatologists commonly use a combination of disease severity (as gauged by the Psoriasis Area Severity Index—PASI), impacts on quality of

life (Dermatology Life Quality Index—DQLI), and contraindications or unresponsiveness to alternative treatments as a way to determine whether a patient with psoriasis qualifies for an expensive biologic. Despite these measures, a disparate distribution of resources still exists.

Inset 8.7

Patient Perspective

A better understanding of clinical trials from the patient's perspective can help industry and investigators understand and overcome some of the hurdles and costs associated with clinical trials. Less than 3 % of subjects with advanced stage cancer participate in cancer clinical trials. Resistance comes from patients, physicians, and insurers. Some trials are abandoned because of a lack of patients. Many trials are being exported overseas because of recruitment and retention issues. Investigators reluctant to recruit volunteers must confront their ethical obligation to better health care in society. By sidestepping participation in clinical research trials or inviting volunteers to participate in clinical research trials, physician investigators are depriving society of the fruits of studies aimed at improving the human condition or the fund of knowledge of human health.

The drawbacks of not encouraging participation in clinical trials are stark. Some trials for rare diseases may never be done. Some populations are underrepresented in trials, for example, the elderly, minorities, and women, pregnant women. The benefits of encouraging participation are equally striking. In the 1970s nearly 95 % of children with cancer were enrolled in clinical trials. By 2000, nearly three quarters of childhood cancers were curable.

Every patient advocacy group encourages subjects to enroll in clinical trials, yet people are resistant to volunteer. The public has negative images of clinical trials from memories of the Tuskegee Syphilis Study, and international trials in Africa where AZT was compared to placebo in HIV patients. People don't want to think of themselves as guinea pigs. They don't want to try something "experimental" or "investigational" because they think it hasn't been proven or won't work. They don't want to be given placebo. The motivation for treatment of some skin diseases (those which are not life-threatening or disfiguring) may be less than for others. They may see the investigator as a selfish opportunist.

Should clinicians enroll subjects in a Phase I trial merely to measure toxicity, and only give a marginal chance of benefit? Most polls show that subjects participating in trials hope for and expect some benefit.

Physicians believe in clinical trials but don't typically enroll subjects. Over 80 % of clinical trial subjects are enrolled by less than 10 % of physicians. The process can be awkward. You don't want to tell your patient that there is

no good treatment, or that you don't know if a particular treatment will work. You don't want to appear that your experience is not sufficient to give a patient an answer. But experience doesn't always help. There are countless cases of longstanding myths in medicine that were debunked by studies. Prior to the 1950s, castration and estrogen were used to treat prostate cancer. A randomized trial showed men in the estrogen-treated group died earlier.

Some patients—and doctors—believe that more treatment is better treatment. But do we know if longer treatments with imiquimod are superior to shorter ones for basal cell carcinoma? Do we know if isotretinoin for 20 weeks is as good as 10 weeks or 30 weeks? Physicians are also reluctant to follow the literature if they have had a bad personal experience. For example, a physician who has seen a life-threatening consequence of dapsone may be reluctant to use it systemically for dermatitis herpetiformis or even topically for acne, despite literature supporting a favorable risk/benefit ratio.

You may be too busy to enroll subjects in studies. You may get no credit for their work. Even as an investigator, you may be unlikely to be listed as an author of trials to which you have made substantial contributions. Instead, authorship may go to marquee lead investigators at prestigious institutions or academic center. You may not like the study design, which may have had little input from you, and may have been put together by committees at pharmaceutical companies with narrow agendas. You may find trials interfere with your practice and disrupt your workflow. You may feel ethically uncomfortable performing clinical trials.

You may not like to give a patient a placebo, or you may feel that the new entity is not superior to the established entity. In Phase III trials, at least, there is already considerable evidence to suggest superiority of the active drug. You may be uncomfortable with your personal gain (money, career advancement, publication) being tied to a research protocol.

But doing trials may make you a better clinician. It may make you more objective and clear-eyed about the limitations of current treatments and the potential for new ones. From an industry, investigator, and patient perspective, encouraging participation in clinical research advances knowledge, and has the potential to bring new and useful treatments to market.

8.8 Conclusion

Dermatology is a field that is particularly vulnerable to ethical issues. It is therefore important to have a strong ethical framework while in practice or conducting clinical trials. The concepts of autonomy, beneficence, non-maleficence, and justice compose an analytical framework for dealing with ethical dilemma. More often than not, researchers inadvertently become focussed on the medicine itself and

neglect that there is a patient on the receiving end. A study looking at 150 papers submitted to the American Academy of Dermatology found that about a third of these submissions lacked any mention of ethics or informed consent [34]. Even if ethics was obtained but not documented in the paper, this startling proportion simply reflects that researchers often neglect the importance of ethics. Ultimately, identifying ethical issues and developing a resolution is a skill that clinicians ought to strive for.

Glossary

Autonomy An ethical principle describing the power that patients have to make their own decisions regarding their own medical care

Beneficence An ethical principle describing the physician's responsibility to act in the best interest of the patient and choose a treatment that would maximize the benefit for the patient

Code of ethics A document set out by an organization which acts as a formal reminder for members within the respective organization to maintain ethical practices

Community equipoise The idea that there is usually uncertainty or debate among experts regarding the gold standard treatment for a certain disease

Conflict of interest An exposure which compromises and biases a physician's decision making ability

Justice An ethical principle suggesting that individuals should have fair access to resources and that these resources be distributed fairly

Medical ethics Moral obligations and fundamental rules founded within the medical field

Non-maleficence An ethical principle that describes the duty physicians have to minimize harm and risk of harm in their patients

Rare disease As per the Rare Diseases Act of 2002, a disease that has a prevalence of less than 200,000 American citizens

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Chapter 9
Clinical Research in Pediatric Dermatology

Christine R. Totri and Lawrence F. Eichenfield

9.1 Pediatric Versus Adult Clinical Research: The Gaps

Scientifically sound clinical research is essential to the practice of evidence-based medicine, with the "gold standard" being randomized, controlled clinical trials (RCTs). However, a review of the literature on standard clinical practice guidelines indicates that the field of pediatrics lags behind adult medicine in the number and extent of such studies, which are necessary to generate the best evidence upon which to base medical and surgical therapies [1]. In general, studies of adults are significantly more likely to be randomized, controlled trials, systematic reviews, or prospective studies of therapies as compared to their pediatric counterparts [2]. In addition, adult RCTs are more likely to be hospital-based and when they are multicenter studies, tend to involve more centers [3]. This information indicates that there are many obstacles in the implementation of pediatric clinical research.

What are the obstacles of pediatric clinical research? Are there different concerns in studying infants, children, and adolescents that make research more difficult? Are there appropriate resources to support the development of pediatric research? Pediatric clinical research has a set of issues that are distinct, including different ethical standards, a federal standard that regulates the risks of children participating in research (the minimum risk standard), subjects that are not considered autonomous,

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Inset 9.1
Chart Review. This is an example of a small study with seminal results which were subsequently reproduced and widely adopted.

This was a multicenter retrospective chart review. One hundred and ten patients with infantile hemangioma were reviewed for outcomes with corticosteroids vs. propranolol. Eighty-two percent of the patients who received propranalol achieved clearance of 75 % or more compared to 29 % of patients who received corticosteroids. Only 12 % of patients receiving propranolol required surgery, compared to 29 % in the corticosteroid arm. The basis of this single study led to recommendations to make propranolol a first-line therapy for treating infantile hemangiomas.

Price CJ, Lattouf C, Baum B, McLeod M, Schachner LA, Duarte AM, Connelly EA. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. Arch Dermatol. 2011 Dec;147(12): 1371–6

and regulations that establish different consenting standards, including consent by proxy, and child/adolescent assent procedures. Furthermore, lack of research infrastructure, limited time and resources to conduct research, and shortages in research staff are also impediments to pediatric research [4]. Yet, these obstacles do not mean that ethically sound, well-designed, and clinically relevant pediatric research should not and cannot be performed. In all medical fields, including dermatology, pediatric patients both require and deserve having evidence generated that can serve as the basis for the highest standards of medical care.

9.2 History of Pediatric Research

Edward Jenner's eighteenth century study on the smallpox vaccination is considered the first documented pediatric study [5]. After Jenner's work, efforts related to immunologic research and the study of vaccinations for prevention of infectious diseases comprised the most common pediatric research. Pediatric subjects were often utilized, as children lacked previous exposure to the infectious disease under study, and comprised the population most at risk [6]. The most successful example of collaborative clinical research advancing clinical practice is probably the work in the field of pediatric oncology, which has had a tremendous impact in decreasing mortality rates in many childhood cancers. For example, acute lymphoblastic leukemia, a cancer with a miserable 25 % 5-year survival rate, has improved to 80 %, largely due to multicentered trials [7].

Inset 9.2

Vaccines

There were regular smallpox epidemics in the United States in 1700s and 1800s. Cowpox scabs were imported from England. The virus was propagated by arm-to-arm transmission (an infected lesion was scraped, and used as a source of vaccine in a recipient).

Edward Jenner, 1798, established widespread vaccination for smallpox. Earlier investigators, including Cotton Mather (1721) showed its benefit in Massachusetts. George Washington inoculated the Continental Army in 1777. Jenner's vaccine was brought to the United States in 1802, and Congress established the first national vaccine agency, directed by James Smith. In 1813, the Vaccine Act was passed to encourage smallpox vaccination and to prevent fraudulent vaccination practices.

James Smith, a Baltimore physician, propagated cowpox for 20 years using the arm-to-arm method every 8 days. In 1821, he accidentally sent smallpox crusts instead of cowpox crusts to North Carolina (NC), causing a smallpox epidemic, and the repeal of the Vaccine Act of 1813.

Vaccines and antibiotics occupy a special place in the history of clinical investigation. Vaccines: fall under the Center for Biologics Evaluation and Research (CBER) purview. Biologics are formed from live tissues and have the potential for contamination. They have complicated and numerous steps for their preparation. The dose response may not be linear. They may not influence Cyt P450. They may be immunogenic. They may be sensitive to minute impurities, even in packaging, viral or a rare unexpected severe immune response.

In 1901 diphtheria antitoxin from horse named Jim became contaminated with tetanus and resulted in 13 children dying. This led in 1902 to the Biologics Control Act (CBER's predecessor), which granted government the authority to license related products and facilities.

In the 1930s, an improperly inactivated polio vaccine led to 20,000 recipients develop polio. In the 1955 "Cutter" incident, insufficiently inactivated Salk polio vaccine resulted in polio in 60 subjects and 89 family members.

Most vaccines are safe, but some claims have resulted in huge liabilities, and manufacturers have stopped production. Developing vaccines is costly, burdened with cumbersome regulation, and fraught with unpredictable outcomes. In 2007, after spending billions of dollars, Merck abandoned the HIV vaccine due to lack of efficacy.

In 1986, Congress passed the National Childhood Vaccine Injury Act (NCVIA), which requires providers to give all recipients risks and benefits of vaccines, and requires them to report adverse events to the Vaccine Adverse Event Reporting System (VAERS). Each year, around 30,000 VAERS reports are filed, and 10–15 % concern serious events (life-threatening, permanently disabling, leading to hospitalization or death). Using funds from an excise tax on vaccines, the national Vaccine Injury Compensation Program (VICP) compensates the injured on a "no fault," basis.

Historically, however, all pediatric research does not have the positive success or legacy of the work done in pediatric oncology. In 1901, there were two isolated, tetanus outbreaks in both St. Louis and in Camden, New Jersey, with the source being contaminated vaccines. The outbreaks led to several deaths which included children, and spurred the development of the 1902 Biologics Control Act, with the premise that the safety of biologics produced and sold by the pharmaceutical industry needed to be better regulated [8]. Also known as the "Virus-Toxin Law," the Biologics Control Act issued regulations mandating routine facility inspection along with requirements for producers to obtain annual licenses for the production and sale of vaccines, serum, and antitoxins [9]. Shortly after, the Food and Drug Act was passed in 1906 which created the Food and Drug Administration (FDA).

Issues surrounding drug safety were addressed with the establishment of the FDA; yet, problems with principled study designs remained. Specifically, the twentieth century was filled with pediatric studies that, in retrospect, are considered unethical. The Willowbrook hepatitis study, in which the subjects, all of whom were institutionalized children, were intentionally infected with the hepatitis virus in order to understand the natural history of the infectious disease [10]. Another controversial research study was seen in the 1990s at the Kennedy Kriger Institute in Baltimore, related to the study of lead levels in children. Critics of the study, which was approved by a John Hopkins University institutional review board, argued that children were exposed to potentially toxic levels of lead and that families were not immediately informed of it [6].

These contentious studies served as impetus for the federal government to intervene to better protect research subjects, including children participating in research. The majority of the guidelines that exist today regarding the protection of pediatric subjects come from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission's recommendations were set into legislation with the Belmont Report of 1979. Among many other guidelines, the document outlines the three core principles that should guide research: respect for persons, beneficence, and justice [11]. Subsequently, in 1983, the Department of Health and Human Services developed specific regulations for the minimal risk standards for pediatric research [12], as will be discussed later in the chapter.

The field of pediatric dermatology is relatively young, and clinical research in the field has been historically limited. Only in 2004 did pediatric dermatology receive specialty board certification in the United States and Canada, the first such subspecialty certification in the world. The field has advanced substantially in the last several years, as reflected in the growth of the Society of Pediatric Dermatology (SPD), an organization devoted to pediatric dermatology which now has over 1,000 members [13]. During this evolution, the field has shifted, from an emphasis on case reports and clinical description, to one attempting to build its research basis, including basic science, clinical and translational research to promote, develop, and advance research in skin diseases in pediatrics [14].

Even with this growth, pediatric dermatologists are facing challenges in research. At the 2007 annual meeting for the SPD, a research task force distributed a survey addressing impediments to the conduction of clinical research. Among the 70 members who responded, 69 of them stated that they had barriers to research productiv-

ity. Inadequate time, funding, training, research infrastructure, and mentoring were considered the main hurdles to research [4]. The end of this chapter will focus on ways in which both as a subspecialty as a whole, and as an individual physician, barriers to research can be minimized and successful research can be achieved in pediatric dermatology. Next, we will delve into some of the unique features of working with children in a clinical research setting.

9.3 Special Considerations

All too often, pediatric care extrapolates from studies done on adults. Approximately 75 % of medications prescribed to children lack adequate pediatric testing [15]. Yet, the physiology, pathology, and psychology of children are all dramatically different from adults [16]. For example, in both adult and pediatric dermatology, topical corticosteroids are the mainstay of anti-inflammatory therapy for conditions such as psoriasis, atopic dermatitis, and other eczematous eruptions. With a higher ratio of skin surface area to body mass, children are at increased risk compared to adults of hypothalamic–pituitary–adrenal axis suppression when they are treated with topical corticosteroids [17].

Unique reactions to medications are also seen in pediatrics. A notable case is with the tetracycline class of antibiotics, which are commonly used in the treatment of acne vulgaris. Specifically, tetracycline, doxycycline, and minocycline are generally contraindicated in patients younger than eight due to the potential for reduction of bone growth and/or permanent tooth discoloration. The discoloration ranges from yellow or gray to brown, is associated with enamel hypoplasia, and is dependent on the dose or type of the drug received in relation to the patient's body weight [18].

Children are more likely to have a paradoxical reaction to antihistamines than their adult counterparts. Antihistamines are often prescribed for their sedating effects in children unable to sleep due to pruritis from certain dermatoses such as atopic dermatitis. Instead of sedation, paradoxical reactions to these drugs manifest as restlessness, irritability, excitation, insomnia, euphoria, or tremor [19]. The examples above are just a glimpse of the dissimilarities seen between children and adults in medicine. Ethical considerations in pediatric research also highlight the differences between children and adults as described in the next section.

9.4 Minimal Risk Standard

In addition to pregnant women, cognitively impaired persons, prisoners, and children are considered a vulnerable population by the Office for Human Research Protections, which is a subsidiary of the United States Department of Health and Human Services. Merriam Webster defines vulnerable as "easily hurt or harmed physically, mentally, or emotionally" and "open to attack, harm, or damage" [20]. Translated in a research setting, there can be concerns about the capacity to comprehend information and to make informed decisions when working with vulnerable

Table 9.1 Codes of federal regulation for pediatric research [22]

Federal category	Requirements needed for IRB approval
§46.404: **Research not involving greater than minimal risk**	1. Research presents no greater than minimal risk; **and**
	2. Adequate provisions are made for soliciting assent of the child and the permission of the parents or guardians
§46.405: **Research involving greater than minimal risk but with the prospect of direct benefit to the participating child involved in the research**	1. Risk is justified by anticipated benefit to the subject;
	2. The relation of the anticipated benefit to the risk is at least as favorable to the child as available alternative approaches; **and**
	3. Adequate provisions are made for soliciting assent of the child and the permission of the parents or guardians
§46.406: **Research involving greater than minimal risk and no prospect of direct benefit to the individual child involved in the research, but likely to yield generalizable knowledge about the child's disorder or condition**	1. The risk of the research represents a minor increase over minimal risk;
	2. The intervention or procedures are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
	3. The intervention or procedure is likely to lead to generalizable knowledge about the child's disorder or condition which is of vital importance for the understanding or amelioration of the child's condition; **and**
	4. Adequate provisions are made for soliciting assent of the child and the permission of the parents or guardians
§46.407: **Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children**	1. After consulting with a panel of experts in pertinent fields along with the opportunity for public review and comment, the Secretary of the Department of Health and Human Services, or his or her designee, determine that either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) the following:
	– The research is an opportunity to further understand, prevent, or alleviate a serious problem affecting the health or welfare of children;
	– The research will be conducted in accordance with sound ethical principles; ***and***
	– Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians

populations. Children are considered vulnerable because of their underdeveloped decision-making capacity [21].

The implications of the label of vulnerability are great, and include special guidelines for protection of these research subjects. From the federal regulation of 1983, a minimal risk standard was adopted in pediatric research. The US federal regulations allow institutional review boards (IRBs) to approve pediatric research based on the standard of minimal risk, which is divided into four categories (Table 9.1) [22].

In general, the first category of the federal regulations allows for participation in research that does not involve greater than minimal risk as long as both parental permission and child assent (when applicable) are obtained. The second category describes research involving greater than minimal risk with the prospect of direct benefit for the subject and, again, parental permission and child assent must be obtained. Research involving greater than minimal risk and no prospect of direct benefit to the subject, but likely to lead to generalizable knowledge about the child's conditions is described under category 3. The risk must only be a "minor increase over minimal risk" as determined by the specific IRB. Finally, category 4 is research not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children as decided by the IRB. Furthermore, for this category, a panel of experts is consulted to review the proposed research plan [6].

The federal definition of minimal risk is based on the risk children face in daily life or during routine examinations or tests [18]. The risk children face in daily living undoubtedly varies from one child to another, leaving room for individual IRBs to interpret minimal risk differently. It was Dr. David Wendler and his colleagues who attempted to quantify this variation by randomly selecting IRB chairpersons in the United States to complete a survey. The survey consisted of 21 questions on topics that included the risk of various research procedures and whether or not different interventions had any direct benefit to subjects. Interestingly, allergy skin testing was categorized as minimal risk by 43 chairpersons (23 %), a minor increase over minimal risk by 81 (43 %), and more than a minor increase over minimal risk by 51 (27 %) [23]. Such results suggest that there are IRBs approving studies while other IRBs are being overly stringent in their interpretation of minimal risk [24].

Inset 9.3

Interventional studies can use something as simple as hot water, or dilute bleach baths.

Volunteers with plantar warts were either treated with hot water or placebo. The feet were soaked for 30 min with each treatments. Treatments were at 44° in the hot water group and 25° in the placebo group. Treatments were administered daily for 3 consecutive days at the beginning, and for 2 consecutive days 2 weeks later. All subjects were assessed 3 months after the start of the study. Over half of the hot water group subjects [53 % (15/28)] were clear of warts, while only a small fraction of placebo-treated subjects were clear [11 % (3/26)].

Local hyperthermia at 44 °C for the treatment of plantar warts: a randomized, patient-blinded, placebo-controlled trial. Huo W, Gao XH, Sun XP, Qi

RQ, Hong Y, Mchepange UO, Li XD, Xiao BH, Lin JP, Jiang Y, Zhang L, Li YH, Xiao T, Chen JZ, Chen HD. J Infect Dis. 2010;201(8):1169–72.

This was a randomized investigator-blinded placebo-controlled trial of 31 patients, ages 6 months to 17 years with moderate to severe atopic dermatitis and evidence of secondary bacterial infection. They were treated with cephalexin and randomly assigned to receive dilute bleach baths and intranasal mupirocin or plain water baths and intranasal petrolatum for 3 months. Treated subjects had reduced EASI scores for the body (submerged in the bath), but not the head and neck.

Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Pediatrics. 2009;123(5):e808–14.

As seen in Table 9.1, category 46.405 and category 46.406 allow for children with disorders or conditions to be exposed to greater than minimal risk. The same ambiguity that applies to the concept of minimal risk is present for "a minor increase over minimal risk" and "greater than minimal risk" as described by these codes. Furthermore, the categories do not allow for the use of healthy pediatric controls in studies that have more than minimal risk, a major obstacle for conducting quality research. Take for example a personal investigator (PI) whose aim is to assess the histopathological differences of the skin of children with atopic dermatitis, during periods of clinical remission, with healthy controls. With the current Codes of Federal Regulation, however, a skin biopsy could not be utilized for the control group as it presents more than minimal risk. Notably, no such federal category exists for adults as they are deemed autonomous and capable of making decisions regarding risk [25]. In other words, in the example given, even if the adult patient will derive no potential benefit from the procedure, the individual should simply be made fully aware of this and given written consent for the skin biopsy.

9.5 Autonomy in Pediatrics

Adults, in general, are deemed competent individuals able to analyze and determine whether or not they are willing to take on the risks of a study in the process of informed consent. In children and adolescents competency varies greatly; and is not only dependent on age, but also on the maturity level of a specific child. In one study, 81 child–parent pairs completed a survey separately in order to assess the willingness to enroll the child in non-beneficial research that posed either mild or moderate risk. Among the paired cohorts, 71 % of children and 72 % of the parents would allow their child to participate in a study that did not benefit the child and posed a risk of a headache. For a research study that was described as one that

would not benefit the child and posed a very small chance of a broken leg, 48 % of the children were willing to participate and 26 % of the parents would allow their child to participate [26].

While it cannot be concluded what percentage of children and parents will agree to participate in a non-beneficial study, some interesting points can be extrapolated from the results. First, the willingness to participate in studies that offer minimal risk is evident from children and parents alike [19]. If appropriate recruitment strategies are utilized by a research team, subjects will partake. Second, the direct concerns and interests of children and adolescents may be different than the parents and even the investigators. This is especially true in disorders or disease states that are decently controlled, treated, or cured with available therapies. Take for example, an investigator who wants to study an alternative treatment for impetigo with the proposed study design requiring 2 weeks of placebo for half of the subjects enrolled. With a readily available, effective treatment alternative such as oral cephalexin, the risk-to-benefit ratio analysis for subjects, their families, and the entire research team is very different compared to a study investigating novel treatment options for life-threatening toxic epidermal necrolysis.

Importantly, the Codes of Federal Regulations do not explicitly address placebo-controlled trials, which are considered the gold standard when studying new drugs. Many believe that if a new treatment is being compared to an active control, rather than placebo, it is difficult to determine the true efficacy of the treatment [27]. While scientifically justified, some argue that withholding therapy is not ethical, such as in the study above, when assessing the efficacy of a novel drug versus placebo in the treatment of impetigo. Yet, the American Academy of Pediatrics (AAP) released "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations," in 1977, 1995, and again in 2010 in which placebo control groups and the ethics surrounding them are addressed. The AAP lists five conditions in which the use of placebo control groups is ethical:

1. When there is no commonly accepted therapy for the condition and the agent under study is the first one that may modify the course of the disease process.
2. When the commonly used therapy for the condition is of questionable efficacy.
3. When the commonly used therapy for the condition carries with it a high frequency of undesirable adverse effects and the risks may be significantly greater than the benefits.
4. When the placebo is used to identify incidence and severity of adverse effects produced by adding a new treatment to an established regimen; or
5. When the disease process is characterized by frequent, spontaneous exacerbations and remissions and the efficacy of the therapy has not been demonstrated [28].

9.6 Consent in Pediatrics

While the concept of consent is well established and understood in research with adult subjects, the translation into pediatrics is not always clear. For the most part, federal regulations allow children to be involved in research only when parental or

guardian permission is obtained, known as consent by proxy. Importantly, for research that is covered by code 46.406 and 46.407 (Table 9.1), permission should be acquired from both parents unless one parent is incompetent, not reasonably available, unknown, deceased, or when one parent has legal responsibility for the care and custody of the child [22]. These requirements of having both parents sign consent forms can be quite limiting, especially with a significant percentage of divorced families in the US population.

Inset 9.4

This is a prospective labor and time-intensive study of a fairly large population which examines a simple, yet important intervention in children. A major source of bias is reporting bias in this study. In this study, 1,812 children ages 2–7 from 78 day care centers in Germany were evaluated. Total body nevi were counted. Parents were interviewed regarding sun exposure and sun protection precautions. There were no significant protective effects of applying sunscreen. However, there was an inverse correlation between the quantity of clothing and the number of nevi.

Effect of sunscreen and clothing on the number of melanocytic nevi in 1,812 German children attending day care. Bauer J, Buttner P, Wiecker TS, Luther H, Garbe C. Am J Epidemiol. 2005;161(7):620–7.

In school aged children, who are developmentally mature, assent from the child becomes important, as it serves to empower children to the extent of their capacity [29]. Assent is defined by Title 45 Code of Federal Regulations Part 46.402 as a child's affirmative agreement to participate in a clinical investigation. Mere failure to object in involvement, in the absence of affirmative agreement, is not enough to be interpreted as assent [30]. Factors that should be taken into consideration when assessing capacity include age, maturity, and psychological state of the patient [31]. The National Commission proposed that all children over 7 should participate in the assent process [32]. Over 35 years later, the AAP still considers 7 as a reasonable minimum age for involving children in the assent process [33].

For the older child or adolescent, assent should play an even larger role. Some even argue that assent in the adolescent should be viewed as an adult informed consent, in an attempt to respect the autonomy of the child, even if parental permission is required [34]. For young adults who are emancipated or have adequate decision-making capacity informed consent should be obtained directly from the patient such as that in the adult counterpart.

9.7 Incentives

Incentivizing participation in research is another important, yet debated topic in pediatric research. Some believe that paying individuals to participate in a study can distort the "volunteer" component of research and can also alter the decision-making of both parents and children [35]. Others argue that subjects are taking time to participate in a study and therefore deserve some compensation for it; to do otherwise, would be unethical. Despite this controversy, nearly 25 % of pediatric trials offer payment and the practice is becoming even more common [36].

Whatever the "right" answer is to the debate, it is clear that children and adolescents are very responsive to monetary incentives. At what age does money begin to matter to a child? This question was addressed in a study in which 42 children and adolescents were interviewed to analyze which factors would influence their decision to participate in research or not. Participants were between 4 and 16 years of age and had diabetes, asthma, seizures, or no chronic medical conditions. Children older than 9 years of age were able to illustrate an appreciation for the role and value of money. These older children had either an accurate concept of the material value of money in society or asked for a realistic amount of money for their participation in a research study, while younger children did not [37]. Pediatric researchers must be cognizant of both the age and maturity level of the children they are working with and adjust accordingly.

There is a lack of uniformity in the definition of the appropriate compensation for participation in a particular study among institutions across the country. Kimberly et al. assessed standards of IRB practices among 69 principal investigators participating in three national, multicenter pediatric clinical trials. No standard among institutions existed; rather, there was substantial variation in subject compensation and assent provided. Compensation ranged widely within and across studies with study 1 ranging from $180 to $1,425, study 2 from $0 to $500, and study 3 ranging from $0 to $100 [38]. Pediatric research, in general, would benefit from a more uniform definition of appropriate compensation across institutions.

In the pediatric dermatology research unit at Rady Children's Hospital-San Diego, the goal is always to make the incentives offered to subjects reasonable, avoiding anything resembling coercion. If possible, subjects receive monetary compensation as reimbursement for all direct research-related expenses such as parking and transportation to and from the research unit. Ideally, the incorporation of medical incentives is used for research participants. As an example, for patients with atopic dermatitis, families are often concerned about whether food allergies may be part of the constellation of atopic findings, or if foods may be specific triggers for their condition. Families may be interested in the results of specific-IgE antibody testing to assist with considerations of allergens, and may consider this an added benefit of blood draws needed for specific research study assessments.

9.8 Creating a Successful Pediatric Dermatology Clinical Research Unit

With all of these issues at hand, several factors play a role in forming a strong pediatric dermatology clinical trials unit. There is no exact formula that works for everyone; yet, there are a few elementary principles that are especially important.

9.9 Mentoring

In all of medicine, there is an emphasis on the importance of mentorship. Mentoring is a way in which established physicians can give back to their particular field of interest. Dedicated mentors have the ability to inspire and evoke a contagious enthusiasm for the field, which often translates positively for the future of the specialty.

The importance of mentorship in medicine was illustrated in a cross-sectional study investigating dermatology residents' loss of interest in academic careers. Of the dermatology residents who responded, 52.6 % reported losing interest in academics due to lack of effective mentorship, role model, or professional guidance [39]. With academic dermatology playing a central role in research in the field, the results of this survey are alarming for the future of research.

Similarly, another survey targeting pediatric dermatologist at the 2010 SPD annual meeting found that the majority of respondents (84 %) believed that mentorship was the most important influence on their decision to enter into a career in pediatric dermatology. The results highlight a possible approach for established pediatric dermatologists to get medical students, residents, and fellows involved in clinical research in a mutually beneficial way. Furthermore, the study suggests that mentorship is an important way in which the field can confront the current workforce shortage [40].

9.10 Collaboration

A large number of conditions seen by pediatric dermatologists are rare, and therefore difficult to study in a single research unit. Epidermyolysis bullosa, for example, is a genetically heterogeneous group of rare disorders caused by mutations involving at least 17 genes that code for dermoepidermal anchoring complex proteins [41]. Even for more common conditions, collaboration can be very important. While AD is frequently seen by pediatric dermatologists, severe AD requiring systemic therapy is not. As such, evidence is lacking for the use and efficacy of the best systemic agents for severe AD, resulting in considerable variation of patient management [42]. Attempting to study conditions such as epidermyolysis bullosa or systemic therapy for severe AD in a single center is difficult as the statistical power needed to show meaningful results in studies is nearly impossible.

Realizing this barrier in research, leaders of the field responded with the creation of PeDRA, the Pediatric Dermatology Research Alliance in 2012. The mission statement of the group is to promote and facilitate high-quality collaborative research with the goal of creating sustainable collaborative research networks to better understand, prevent, treat, and cure dermatological diseases in children [43]. Thus far, PeDRA has four groups including the hemangioma investigator group, the inflammatory skin disease collaborative, epidermolysis bullosa clinical research consortium, and disorder of cornification working group. The hemangioma investigator group, for example, has collaboratively published over 40 studies since its establishment in 1999 [44].

9.11 Ethics and Relationships

There must be a strong ethical approach from everyone involved in a research unit including the research coordinators, clinical fellows, and ultimately the PI. When recruiting pediatric research subjects, the potential impact is not only on the patient but the entire family. Trials must be carefully selected as to abide by the ethics that form the foundation of the research unit.

Forming strong relationships is another element needed for strong research unit; whether it is with the physician referral base, the general community that serves an important role in recruitment, or the potential subjects themselves. For the latter group, an alliance built on trust must be made with the caregivers of the child in order to ensure adherence to the study protocol from the child.

Having a dedicated research staff that is child and adolescent friendly is also helpful in carrying out pediatric dermatology research. When possible, it helps to build a research team with administrative support and nursing staff who are willing to be flexible with scheduling, allowing families easy access for visits. Junior faculty need to learn the processes of protocol development, budgeting, IRB submission, among many other things. Yet, having a dedicated research administration staff can greatly facilitate successful transfer of ideas to studies, and dedicated research nursing facilitate the completion of a study [45].

Locked, dedicated research space is also very helpful, allowing the secure placement and storage of study materials including subjects' identifying information. When working with children, having movies playing on DVDs and computer access for the subjects can also be essential. This is especially true with long visits such as the ones needed in pharmacokinetic studies which often run from 8 to 12 h.

9.12 The Future of Pediatric Dermatology Clinical Research

Building a successfully run, pediatric dermatology research unit is essential to conducting important clinical research. Yet, as an isolated entity, only so much can be accomplished. Collaboration with colleagues in not only one's field, but also other

specialties, is critical. Furthermore, if the gap between adult and pediatric research is going to close, support needs to come from changes in federal legislation that prioritizes research in children. Steps in the right direction have and continue to be made. In 2012, President Obama signed into law the FDA Safety and Innovation Act which included the Rare Pediatric Disease Priority Voucher Program, awarding priority review vouchers to sponsors of rare pediatric disease product applications [46]. Furthermore, as recently as November of 2013, the President signed into law the National Pediatric Research Network Act.

Provisions of the law include:

1. The authorization of the establishment of a national pediatric research network to better support pediatric research.
2. Funds can be awarded to support basic, clinical, behavior, or translational research as well as the training of researchers in pediatric areas with unmet needs.
3. An appropriate number of awards will go to research focused primarily on pediatric rare diseases or conditions and ensures to coordinate multisite clinical trials of studies focused on the prevention, diagnosis, or treatment of these rare conditions.
4. The establishment of a data coordinating center to distribute findings and aid in collaborative research projects [47].

Legislative breakthroughs such as these suggest a bright future for pediatric dermatology clinical research. From a clinical point of view, there are still many questions left unanswered for conditions such as atopic dermatitis, psoriasis, and rare genetic diseases. With the appropriate advocacy from legislation, along with diligent and resolute researchers focused on collaborative efforts, it is hoped that research will continue to work to answer these questions.

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Chapter 10
Statistics

Enzo Emanuele

10.1 Introduction

Clinical trials are expensive to conduct but are nevertheless a key component in the practice of evidence-based medicine. They are carried out to collect data on the safety and efficacy of new treatments for existing medical conditions but they are exceedingly expensive to conduct. For example, of the $46.4 billion spent by Pharmaceutical Research and Manufacturers of America companies in 2010 on research and development, $32.5 billion (70 %) was spent on clinical trials. Recently, it has been documented that clinical research accounts for more than 30 % of the total NIH budget ($10.7 billion out of $30 billion in 2010) of which a major component ($3.2 billion) is expenditure on clinical trials. In simple terms, this translated in 2011 into a grant cost per patient of approximately $16,500 per study. However, the cost of delaying a new treatment is incalculable [1]. Much thought should be put into the design of a trial and only then should a protocol be developed to ensure that the targeted outcome is successfully achieved. It is vital to produce thorough documentation of the proposed conduct of the study, as this will smooth the progress of regulatory approvals.

A clinical trial can be conducted using healthy volunteers or patients, depending on the type of intervention. Trials are designed to establish more effective therapies for a wide range of medical conditions but one caveat is that they also have the potential to expose participants to unknown risks. Furthermore, biased knowledge extracted from fundamentally flawed clinical trials may actually lead to the unintended harm of patients treated subsequently by the new therapy. Although running a well-designed clinical trial may appear a relatively straightforward task, the underlying protocols can be flawed unless founded on meticulous methodology [2].

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A number of dermatologic clinical trials with less than satisfactory outcomes have been reviewed by Williams and Dellavalle in 2012 [3]. The purpose of this chapter is to provide a brief guide to some factors that need to be considered when designing a clinical trial, with particular emphasis on dermatology.

10.2 Have We Learned from Our Errors? Pitfalls of Clinical Trial Design in Dermatology

Cutaneous leishmaniasis (CL) is a skin condition caused by infection with *Leishmania* parasites but inadequate design of trials to assess the effectiveness of treatments for CL has made much of the data invalid [4, 5]. The randomized controlled trials (RCTs) discussed assessed a broad range of treatments and many different clinical questions but the results provided limited opportunities to describe and pool important data. Concerns were expressed regarding the precision of data reported in several of the studies. Furthermore, because the majority of RCTs had a high risk of bias (Table 10.1), it was difficult to conclude whether one treatment was more beneficial than the comparator much of the time. Many interventions discarded as ineffective in an essentially inconclusive study, could still prove to have some benefit if they were evaluated in an adequately powered study. Critical errors reported ranged from the inadequacy of study design, trial conduct, analyses, and data reporting [6]. The conduct of these trials was not warranted but illustrates that an accurate design, planning and implementation of a clinical trial is of paramount importance. The design and reporting of RCTs can be greatly improved, by adopting general guidelines and rigorous peer-review checks in journals. Other factors that affected the validity of these trials were the parasitological confirmation and determination of the causative Leishmania species, the use of longer duration designs, and clinically understandable and patient-orientated outcome measures [6]. The authors concluded after analysis of the methodology that potential bias could make it difficult to determine whether effective therapies exist for CL. Weaknesses were found in the adequacy and transparency of randomization, loss of participants, causative Leishmania species, outcome measures, and follow-up times. Given these distorting effects on the evidence base, the authors proposed for the conduct of clinical trials that aimed to develop effective therapies for CL [6].

10.3 Importance of Randomized Controlled Trials (RCTs)

RCTs are recognized as the "gold standard" to assess the effectiveness of new interventions but there is some disagreement [8, 9]. Nevertheless, a series of RCTs in dermatology have been collated into an online database of dermatological eczema trial results [10]. It is now considered unsafe to rely on data from a single RCT, not

Table 10.1 A common classification scheme for bias [7]

Type of bias	Description	Relevant domains in the collaboration's "risk" of of bias tool
Selection bias	Systematic differences between baseline characteristics of the groups that are compared	• Sequence generation
		• Allocation concealment
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest	• Blinding of participants and personnel
		• Other potential threats to validity
Detection bias	Systematic differences between groups in how outcomes are determined	• Blinding of outcome assessment
		• Other potential threats to validity
Attrition bias	Systematic differences between groups in withdrawals from a study	• Incomplete outcome data
Reporting bias	Systematic differences between reported and unreported findings	• Selective outcome reporting

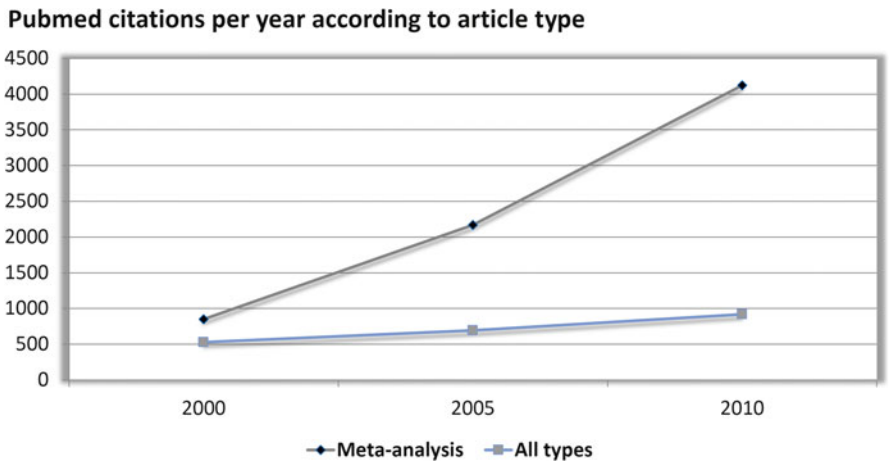

Fig. 10.1 Annual citations of meta-analyses in PubMed compared with all publication types [8].

because it is unsafe for the patient but rather because it may not be well controlled. Nevertheless, if a single RCT is large enough and well controlled, it should provide adequate evidence to support the tested hypothesis. However, there can be no doubt that systematic reviews (SRs) that collate information from many studies provide a more reliable body of evidence. SRs that connect data from different trials are referred to as meta-analyses, and often reveal answers to questions that may be overlooked in separate studies [3, 11]. They are an essential tool for providing collated trial results to healthcare professionals as they identify the best therapy for a specific disease. SRs minimize bias by considering all of the available literature (Fig. 10.1). A significant drawback of SRs is that they require substantial work to

conduct and crucially keep them up to date, despite their admirable and exhaustive assessment of relevant data.

When designing a clinical trial it is important to decide whether it can be linked to other studies and thus obtain a general consensus about the effectiveness of a new intervention.

10.3.1 Issues to Consider When Designing and Implementing a Clinical Trial in Dermatology

It goes without saying that clinical trial design should follow standard good clinical practice for the benefit of all subjects involved. In the final analysis, the duty of patient care must hold sway over all other considerations even if it is to the detriment of the study. It is vital that sound methodological principles are implemented from the outset and it is strongly advised that the input of a statistician be sought. Fundamental issues that must be considered include the principle of clinical equipoise, selection of participants, type of trial, and power calculations. It is essential to have hard endpoints in the trial (e.g., objectively measurable, clinically relevant endpoints) and not to do preliminary sub-analyses if possible. The trial must be designed in such a way that unequivocal conclusions can be drawn. An independent advisory board should hold sway over the conduct of the clinical trial to curb any "over enthusiasm" of the personnel conducting the trial. A current example of clinical equipoise in dermatology is the treatment of bullous pemphigoid with either prednisolone or tetracyclines [12].

10.3.2 Methodological Considerations in Clinical Trials

A common type of clinical trial is conducted to test the effectiveness of an established treatment regime over a newer therapy. A flow chart of such a trial is shown in Fig. 10.2 [13].

This chart provides a graphical picture of a trial plan from beginning to end. This is a good example of a clinical trial for several reasons:

- There is a clearly defined primary and secondary objective
- Well-documented criteria for selection of participants
- The interventions are clearly described
- Implementation of randomization and blinding (masking)
- Appropriate sample size and statistical analysis
- Assessment of the cost-effectiveness of the interventions

Next, some of the factors that should be considered before embarking on a clinical trial are discussed.

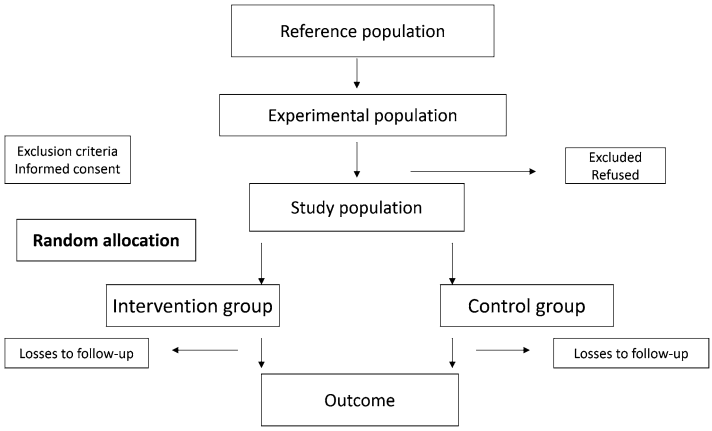

Fig. 10.2 Flow chart of a clinical trial

10.4 Ethical Considerations

Ethics in human research were considered only after the dreadful medical experiments carried out by the Nazis came to light. As a result, ten basic principles of human research were formulated in the Nuremberg Code of 1949 [14] that was later developed into The Declaration of Helsinki and accepted by the World Medical Association [15]. A phrase introduced in 1987 by Freedman [16], "clinical equipoise" was coined to describe a medical dilemma that can arise during a clinical trial. A trial starts with the assumption that it is not known if the intervention being tested will be more effective than the existing one. The problem occurs when it is obvious that one treatment is much more effective than another. Thus, there is an ethical necessity for the investigating clinicians to provide the improved treatment to all participants.

10.5 Importance of Informed Consent of Participants in a Clinical Trial

Informed consent is mandatory and the consent form must clearly state [17, 18]:

- It is a research study including the purpose, duration, risks, benefits, and alternatives to the intervention being studied
- That participation is voluntary
- Confidentiality will be rigorously observed
- Contact details and information will be available if a subject has questions or concerns about the study

Interestingly, these safeguards are not flawless. This is because the clinician running the trial necessarily has incomplete knowledge regarding the risks and benefits of the intervention because they are not known.

10.6 Integrity of Findings

It is important to realize that there is some evidence that industry-funded trials have tended to report favorably on new drugs (human nature being what it is, loyalty to the sponsor, etc.). Therefore, all trial researchers involved in a trial must be completely impartial.

10.7 Statistical Considerations

It is vital to collaborate with an experienced statistician who will help with the design of the trial and assist in selecting an achievable outcome. A statistician's input is invaluable in deciding many factors including an appropriate sample size, randomization protocols, and the overall analysis of trial results following data collection. Bhardwaj and colleagues [19] laid down sound statistical criteria that should be considered in the design of a dermatological clinical trial. They concluded that studies that claim clinical relevance may actually lack sufficient statistical significance to make the conclusion true and, conversely, that a study purporting to show a statistically significant difference between two interventions may lack expediency. The power of a statistical study is the probability of detecting a difference when one exists. Bhardwaj and colleagues [19] explained the importance of power by using specific examples taken from the dermatological literature. It is vital to understand the direct relationship between sample size and power when drawing conclusions. The failure to detect a clinically important difference between two groups can occur as the result of inadequate sample size; that is, inadequate power [19–21]. This difficulty will most likely arise in studies of rare medical conditions, but it can also be a hindrance to studies involving more common ailments. As the power of a statistical study increases, the ability to detect progressively smaller differences also increases. Therefore, the perception of a particular study having too much power must be considered. In contrast, studies with very large sample sizes may detect statistically significant differences that are not clinically relevant [19].

Inset 10.1

Statistical Methods

In the 1930s, Sir Ronald Aylmer Fisher introduced statistical methods to research including randomization, and analysis of variance. Around the same time, Torald Sollman added placebo arms and blinding to studies. One of the challenges of increasingly complex clinical trials and pooled trials is reproducibility. One of the best ways to maximize validity and reproducibility is to minimize statistical bias and statistical error. Scientific journals are now adding statisticians to their editorial boards. Their task is to rigorously scrutinize the statistical methodology of high profile studies.

The concept of power in a clinical trial refers to the probability of detecting a difference between study groups when a true difference exists. This statistical power is undermined if the number of participants in each study is too small to identify important differences that may exist. In contrast, a study can be overly large and spuriously identify differences that are not actually clinically significant [19]. Thus the purpose of statistical analysis is to determine whether the findings are due to chance rather than to genuine differences between the treatments. What could be worse than carrying out a large-scale clinical trial, only to be told that there were fundamental flaws in its design and therefore the conclusions.

To recap, a small study that claims clinical relevance may lack sufficient statistical power to justify its conclusions. Conversely, authors of a study may speak of the statistical significance of a treatment effect that has little, if any, clinical efficacy. Therefore, when evaluating the validity of a study, the intelligent reader must consider both the clinical and statistical significance of the findings. There is a wealth of literature available to the interested reader that describes the mathematical basis of the statistics required for a clinical trial [19–24]. Important factors to consider are the values of the type one error rate, α, and power, $1-\beta$ (i.e., how mathematically exacting the study will be), as well as the expected improvement to be detected, which will determine the sample size of the study. Reliable efficacy data are required because if the estimate of the efficacy of the comparator treatment is wrong, the results of the study may be underpowered, hence failing to produce the intended results. In the study highlighted in Fig. 10.2, a total of 140 patients (randomized 1:1 to prednisolone or ciclosporin) gave the study about 80 % power [13]. This sample size also allowed for an approximate 10 % loss of patients to follow-up after 6 weeks of the trial. The outcomes of any trial, whether objective or subjective, must always be reliable and provide meaningful measures. Statistical techniques that can be used to analyze trial outcomes include logistic regression for dichotomous endpoints, Poisson regression for rates, Cox regression for time-to-events, and linear regression for continuous measures e.g., the weights of participants [1].

10.8 Selection of Participants

For a clinical trial to be successful the selection of an appropriate study population is crucial. Even if all participants volunteer for the intervention, the enrolled cohort may differ from the general population. This can inadvertently lead to a bias in selection known as “volunteer bias.” Many factors may be involved including the trial criteria for inclusion, intrinsic attributes of the subjects or deliberate exclusion of a potential participant because the investigator subjectively believed that their overall prognosis might be detrimental to the trial. Without a suitable cohort of participants, the measure of the success of an intervention may not translate into useful new clinical therapy [2].

10.9 Write a Detailed Clinical Trial Observational Plan

One important methodological consideration is to have a well-thought-out protocol available. Its purpose is to provide all personnel involved in the trial with documentation that should:

- guide the conduct of the trial
- give participants a detailed description of the methods used
- inform review boards of predefined safeguards to protect the safety of the participants
- permit potential funding bodies to assess the research proposal
- provide peer reviewers with a report of pre-specified methods designed to evaluate potential bias [25]

To fulfill the above purposes, the protocols should be detailed and transparent. Often protocols do not adequately describe methodological details such as allocation concealment, primary outcomes, power calculations, and the roles of sponsors and investigators in the trial. Apposite randomization rests on adequate allocation concealment, which ensures that clinicians and trial participants are unaware of the treatments. Without allocation concealment, random allocation sequences can be circumvented undermining the crucial unbiased nature of RCTs [26]. Selection bias refers to the possible differences between baseline characteristics in the groups under comparison. Investigators should devote appropriate resources for allocating interventions to participants on the basis of some chance (random) process and report their methods clearly, avoiding nonrandom methods of allocation. Adequate generation of the randomization sequence takes little effort but undoubtedly increases the degree of scientific accuracy and the credibility of the trial. Inadequate allocation concealment leads to either an underestimation or an overestimation of the efficacy of the treatment under investigation. If these safeguards are not implemented, exaggerated descriptions of the effectiveness of interventions can be made. A lack of transparency and incomplete description of methods makes critical assessment of trials difficult. Therefore, the Delphi consensus was developed to provide useful information to guide the development of trial protocols [25].

10.10 Assessment of Data Quality and Guarding Against Bias

Quality assessment should include an evaluation of the trial plan designed to safeguard against bias. They include methods involved in the generation of the randomization sequences and allocation concealment of trial participants. Particular attention must be paid to who should be "blinded." Sometimes, it is important that certain investigators have more information than others, the relevant people being the outcome assessors, the presiding clinicians and of course the participants.

Another issue that can bias trial results is lack of reporting of the number of participants lost to follow. Clearly, they could be the subjects who did not respond to the intervention making the results for the remainder of participants more significant than warranted. The control and intervention groups should have (as far as is reasonably possible) substantial baseline comparability. When the results from a single RCT are written up for publication in a scientific journal of high repute, great care must be taken by the authors to show complete impartiality. Thus, there are many pitfalls in the planning and running of an authoritative clinical trial. It is instructive to study the approaches adopted in the excellent multicentre dermatological clinical trial highlighted in Fig. 10.2 [13].

Inset 10.2

Reproducibility

One of the concerns about clinical research is the difficulty in reproducing results. Most successful studies of new compounds show either non-inferiority or mild—albeit statistically significant—benefit. Moreover, while initial studies of a new drug or device show a dramatic effect, subsequent work demonstrates an attenuated benefit.

A number of investigators and pharmaceutical companies have observed repeated instances of this phenomenon. In 2011, Amgen attempted to repeat 53 landmark cancer studies. They were only able to reproduce six of the studies. The following year, Bayer tried to reproduce 67 studies in oncology, women's health, and cardiovascular disease. They were only able to reproduce 20 % of the trials. Other companies such as AstraZeneca and Novartis have encountered the same problem. Similar concerns have been raised by device manufacturers.

Some of this drop-off has been attributed to a statistical phenomenon known as regression to the mean. However, regression to the mean is only one possible explanation for the so-called "crisis of irreproducibility." Other reasons cited include: flawed study design; flawed data analysis and interpretation; incompletely documented materials or methodology in the protocols or publications; omissions of key aspects of a protocol in publications; incompetence; deception; a bias to exclude negative results; and including only sensational or blockbuster data subsets in order to appeal to high-impact journals. There may also be pressure in companies and the scientific community to adequately criticize flaws in studies for fear of retaliation.

For example, even though there are many regulations governing human research in the United States, studies (Martinson et al. Nature 2005;435:737–738) show that 0.3 % of surveyed scientists reported ignoring major aspects of human research requirements, and 7.6 % skirted minor requirements. Online courses, workshops, and webinars have been developed to make training as accessible as possible.

So much money, time, and effort are spent on clinical trials, and so many trials are built on a foundation of previous trials that errors and inaccuracies and irreproducibility in trials can create a crisis of confidence in the whole clinical research enterprise.

In January 2014, the President's Council of Advisors on Science and Technology (PCAST) met at the National Academy of Sciences to discuss the crisis of data reproducibility. Organizers declared that the inability to reproduce results threatens to collapse the edifice of science. Scientists are rewarded on their track record of publications, especially in high-profile scientific journals. These journals often seek simple compelling stories. The more publications scientists get, the greater their ability to recruit funding, research staff, and promotions, including academic tenure. Because of these pressures, one participant recommended changing the culture of scientific journals and funding agencies.

Regression to the mean often occurs because of statistical bias. Data for a device or drug are selected for outliers so that they achieve statistical significance. These studies are published. If the significance is on one extreme, subsequent measurements will be closer to the average. When the effect is tested on the general population, which has not been pre-selected for certain inclusion and exclusion criteria, the impact of that effect is significantly reduced. Adding an unbiased statistical team to study design and data analysis can reduce the phenomenon of regression to the mean, or make investigators aware of its likely centrality to an observed result.

Comparative effectiveness research may also reveal studies which are difficult to reproduce or which have little significance in improving quality of life for patients. Skin, being a visible organ, readily assessed by patients, is a ready target for the evaluation of effectiveness of dermatologic therapies. A recent article (Journal of the American Academy of Dermatology, 68(1):64–72, January 2013.) examined patient preferences for various psoriasis therapies. Patients are likely to simultaneously factor in cost, convenience, side effects, and effectiveness. Canvassing clinicians for their views on the effectiveness of skin disease therapies (Journal of the American Academy of Dermatology, 68(2):262–9, August 2012) is a secondary avenue for comparing the quality of published research and its impact on patients' lives.

One of the recommendations of the meeting was to scrutinize controversial publications after they were in print or online, with particular attention to systematic errors that could alter outcomes. Data transparency and the availability of all raw data were also strongly recommended. Sometimes data are withheld for lack of space, or because the investigators do not feel they are pivotal to their conclusions. Sometimes data and evidence are assumed to be common knowledge, and not published, yet such knowledge may be common only to the investigator, or a small cadre of narrow specialists. Some results cannot be reproduced because of the inclusion of false positives and false negatives.

Furthermore, data cannot occasionally be reproduced because all the factors affecting an outcome are unknown. For example, we are only now learning that the skin has a microbiome of thousands of species, which vary by body location, diet, locale of residence, and skin health/disease. The microbiome is complex and interacts with the skin as an epigenetic influence on skin biology.

Scientific journal editors recommended rewarding investigators who routinely generated reproducible data, while withholding funding and other rewards from investigators whose data could not be reproduced. They are recommending additional members to journal boards of reviewing editors who are trained statisticians. They are recommending a statistical plan for handling data before any experiments are done, rather than ad-hoc during the study. Randomization, appropriate sample size, and blinding are being recommended for clinical studies.

Editors of prestigious journals are creating guidelines to minimize the likelihood of irreproducibility, but claim they are under pressure as well from alternative publications and online publications.

Reproducibility can fail because the original report was incorrect, or because of an error (intentional or unintentional) in conducting the science. Transparency in the conduct of the experiments, including greater space for detailed materials and methods may help address errors in reproducibility which occur because intellectual property or lab or corporate secrecy prevent full disclosure of proprietary steps and reagents.

Interestingly, the majority of the failures occur in preclinical research. One suggestion was made to have preclinical trials emulate the standards and practices of human subjects clinical studies.

Some critics have encouraged funding to test the reproducibility of trials. For example, the Reproducibility Initiative is studying 50 high-impact oncology studies, at an expected cost of $1.3 million, coming from private funds. It is unclear if the NIH is interested in funding reproducibility of research.

A clinical trial is typically designed to assess whether a proposed new intervention is better than an existing treatment. Figure 10.2 is a schematic illustration of a two-arm, observer-blind, parallel-group, RCT with the primary objective of determining the effectiveness of drug A versus drug B. In any trial, a variety of secondary outcomes should also be assessed including the improvement in the ailment, pain reported by subjects and the overall improvement in their health, and therefore quality of life. It should be emphasized that the quality of life is becoming more and more important to payors of health care. The measurement of health-related quality of life (HRQoL) in dermatological patients is now recognized as an important step in the knowledge of the burden that skin disease may pose on patients. HRQoL has become an essential outcome parameter in RCTs [27]. Any treatment failures and adverse reactions to drugs should be meticulously documented. With health budgets under severe constraint, the cost-effectiveness of using a potentially much more expensive treatment should be taken into account [9].

Inset 10.3

Negative Results

These are examples of dermatology studies which reported negative results.

One of them is a single center randomized prospective double-blind placebo-controlled trial of subjects treated with etanercept 50 mg SQ twice weekly for 12 weeks compared to placebo.

Treatment of hidradenitis suppurativa with etanercept injection. Adams DR, Yankura JA, Fogelberg AC, Anderson BE. Arch Dermatol. 2010;146(5):501–4.

This MultiCenter Trial Phase II Reported Negative Results

This was a double-blind placebo-controlled phase II trial of 28 subjects with scleroderma or morphea covering greater than 20 % body surface area. They were randomized to receive either imatinib mesylate or placebo for 6 months, and then evaluated 6 months after discontinuation of study drug. Quality of Life was measured (DLQI Dermatology Life Quality Index, and HAQ Health Assessment Questionnaire) as well as Rodnan Skin Scores, and pulmonary function tests. No difference in efficacy was noted between the placebo or the treatment group.

Prey S, Ezzedine K, Doussau A, Grandoulier AS, Barcat D, Chatelus E, Diot E, Durant C, Hachulla E, de Korwin-Krokowski JD, Kostrzewa E, Quemeneur T, Paul C, Schaeverbeke T, Seneschal J, Solanilla A, Sparsa A, Bouchet S, Lepreux S, Mahon FX, Chene G, Taïeb A. Imatinib mesylate in scleroderma-associated diffuse skinfibrosis: a phase II multicentre randomized double-blinded controlled trial. Br J Dermatol. 2012;167(5):1138–44.

10.11 Criteria for Inclusion of Subjects in a Trial

It is important to recruit a suitable number of participants (vide supra, Sect. 10.7) so that meaningful conclusions can be drawn. The physician in charge of the trial will recruit patients who have been diagnosed with the condition being investigated. If there is doubt about the diagnosis, an expert panel should provide additional assistance. Potential subjects may be excluded for reasons including pregnancy and previous exposure to medications that may interfere with the trial. In other trials, healthy volunteers are recruited to provide a pharmacokinetic profile of a new drug in humans (to compare with laboratory animal studies).

10.12 Methodological Considerations Concerning Interventions

Participants should be selected by a randomization algorithm to receive either drug X or drug Y up to a maximum dose agreed before the start of the trial. Permission is usually granted to adjust the dosage according to the clinical response but ideally the dose of a drug should not be altered during the first few weeks. Participants should not use alternative therapy that could affect the outcome of the trial but regular medication for other medical conditions can be continued. Participants in the observational arm of the study act as the control group and should receive their normal therapy as required.

10.13 Clinical Trials Involving Rare Dermatological Conditions

Large-scale RCTs are difficult to conduct for rare ailments such as pyoderma gangrenosum (PG), an inflammatory disorder of the skin. The rarity of PG means that there is a paucity of published clinical trial data on its treatment. Commonly used interventions have not been formally assessed, clinical practice being based on hearsay and practical experience rather than unequivocal trials evidence. The approach to address this lack of evidence is to carry out a RCT of the two commonly used systemic treatments, namely prednisolone and ciclosporin. The UK Dermatology Clinical Trials Network's STOP GAP Trial was designed to address this lack of clinical trial evidence. It is instructive to follow the approaches adopted in this well-thought-out trial to understand good practice when designing a clinical trial in dermatology [13]. The methodological approach was to set up a multicentre trial involving 50 UK hospitals with just a few patients from each of them. In this manner, a definitive dermatological clinical trial can be conducted for a rare disease, which would not be possible in a single institution. This is an example of a superiority trial, with prednisolone as the control intervention but why was this method chosen? The decision to power the study on the basis of superiority was because:

- ciclosporin is much more expensive than prednisolone (so has to be much more efficacious than prednisolone to justify its use in clinical practice)
- case series and clinical experience suggest that ciclosporin may gain control more quickly, and have fewer side-effects in long-term therapy
- a pragmatic approach due to the costs associated with funding a much larger worldwide trial

The STOP GAP trial is a unique study that could not be achieved without the collaborative efforts of large numbers of participating dermatologists and other healthcare personnel. This trial is methodologically interesting in that efforts were made to include all PG patients who are willing to take part, by inclusion in either the RCT or the observational study. It is a good example of how to link a trial to other studies in order to gain a general consensus about the clinical findings [13].

10.14 Executive Overview of a Clinical Trial

An independent committee must always be appointed to oversee a clinical trial. For example, the steering committee for the PG trial included an independent chair and three other independent members (one of whom was a patient). All members were independent of the study team, although the Trial Manager and some other members of the Trial Management Group were permitted to inform the committee about progress [13]. In all trials, international standards on institutional oversight of trials should be followed as stipulated, for example, by the US Food and Drug Administration (FDA) [26].

10.15 Characteristics of Successful Trials

When the methodology underlying successful clinical trials is analyzed, certain common characteristics emerge. First, the trial was conceptually simple, customized to fit a well-defined group of patients and address questions of clinical relevance where genuine doubts about the most effective treatment existed. Second, unnecessarily complex participant entry criteria and data requirements were avoided to ensure that the trial data were generally applicable in general clinical practice. Third, a well-thought-out control arm was chosen and allocation concealment measures were made as secure as possible. Finally, great care was always taken over the blinding of the intervention and outcome assessments. These are useful goals to think about when designing a clinical trial but there is still scope for further improvement. An example of a successful and well-conducted clinical trial is one that investigated the effects of ceftaroline on complicated skin and skin-structure infections (cSSSI). Ceftaroline is a broad-spectrum cephalosporin prodrug that is effective against a wide range of bacterial infections. In the trial, it produced high clinical cure rates, was efficacious against cSSSI caused by MRSA and other common pathogens, and the drug was well tolerated. The authors concluded that ceftaroline has the potential to provide a monotherapy suitable for the treatment of cSSSI [28].

Insert 10.4

Compliance

Lack of compliance may be another cause of Regression to the Mean. Lack of compliance can be assessed on medications by weighing tubes, or having a cap sensor. It can also be assessed on devices such as phototherapy units. Typical studies show a "sawtooth" graph of compliance, with compliance gradually increasing just before a clinical office visit, followed by a rapid taper until the next visit.

Adherence to topical therapy increases around the time of office visits. Feldman SR, Camacho FT, Krejci-Manwaring J, Carroll CL, Balkrishnan R. J Am Acad Dermatol. 2007;57(1):81–3.

The utility of a data-logging device for measuring adherence to home phototherapy. Yelverton CB, Balkrishnan R, Feldman SR. Photodermatol Photoimmunol Photomed. 2006;22(5):270–2

10.16 How to Improve Dermatological Clinical Trials

One valuable approach is to hold consultations with patients who have the condition and have been treated by current therapy. Patient involvement in clinical trials planning should be tackled if dermatological trials are to reflect truly the topics of concern to patients [24]. Traditionally, patients are rarely seen as active partners in the research; rather they are just the subjects of the clinical research. The active involvement of patients or their representative organizations in a clinical trial is a relatively new development. This topic has been well-documented and there are advantages of patient involvement for both the research itself and the patients [29].

The benefits for patients are (from Ref. [29])

- Patients gain knowledge and a better understanding of the research
- Greater self-esteem and confidence of the patient representative that is involved in the process
- Making use of their experience and knowledge on their condition
- Acceptance of patients as equal partners in the clinical trial process and the creation of a sense of ownership of the research
- Access to funding for bringing researchable topics to the research agenda that otherwise would not be taken into consideration
- Increased understanding of the nature and purpose of a clinical trial
- Create a bridge of understanding between patients and researchers
- Health care and therapies that are more representative of patient's "real" needs

Fig. 10.3 Research wastage can occur at several stages along the research development pathway

The benefits for the research are:

- Changes in information material given to patients.
- Changes in the design of the study and aspects of research such as: ways of collecting data, analysis of qualitative data, research questions, -tools, -priorities and -outcomes.
- Increased recruitment and better recruitment strategy.
- Increased response rates.
- More patient-relevant research findings and methods.
- Challenged the assumptions made by researchers.
- Wider dissemination of findings.

The take home message is that the clinician should try to understand what patients are seeking in a new intervention and use this feedback when designing a trial; after all, it is supposed to be for their benefit.

It is very important to avoid selective outcome reporting bias. This can be achieved by prospectively publishing the clinical trial protocol and primary outcome measures in a publicly accessible trial register before the study is completed [25]. Many trials have too many outcome measures that have not been tested rigorously [26]. The potential pitfalls are starkly summarized in Fig. 10.3.

Collaborative work with countrywide and international dermatology trial networks is highly desirable if large numbers of patients with less common conditions are to be studied [13]. Hospital collaboration with academic clinical trial units will undoubtedly improve the professionalism and conduct of dermatology trials. It is especially important to note that many clinical trials in dermatology are outpatient based because many patients are ambulatory. Again, to increase numbers of rare skin diseases studied, a multicentre clinical trial can be coordinated relatively easily. For example, a study of prophylactic antibiotics to prevent cellulitis (erysipelas) of the leg involved the recruitment of some 400 patients many of whom were identified in outpatient clinics [30].

10.17 Concluding Remarks

The first duty when considering the methodology to be used in a clinical trial is to ensure the safety of the participants (patients and healthy volunteers). Ethical principles and practices should guide the physicians running the trial, which should be designed and conducted in such a way that the reliability of the data is of the highest possible standard. An experienced statistician should be consulted before the trial commences. Suitable endpoints, methods of comparison, and statistical analyses must be carefully selected to achieve the intended goals of the research. A well-designed RCT is a powerful method to demonstrate significant differences between the efficacies of different interventions and ideally should lead to better therapies for a wider cohort of patients. To this end, the selection of participants with narrow enrollment criteria must be balanced with the intent of translating the trial findings to the general population worldwide. It is now considered better practice to use SRs rather than rely on a single RCT.

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Chapter 11
Photography

Adam Blechman and Anar Mikailov

A film is never really good unless the camera is an eye in the head of a poet.

Orson Welles

11.1 Introduction

Visual context is a cornerstone of medical education, particularly in dermatology, where diagnoses require visual inspection. The earliest types of medical artwork were drawings of patients with signs of disease. The *Tractatus de pestilentiali scorra sive mala de Franzos* of Joseph Grunpeck from 1496, depicted people with Syphilis; it is likely one of the earliest dermatological illustrations [1]. In 1798, Robert Willan created his book *Description and Treatment of Cutaneous Disease*, with the help of several artists, to draw the seminal morphological scheme for the classification of skin diseases [1].

One of the first methods of photography was the daguerreotype, named after its inventor, Louis Jacques Mande Daguerre, in 1840. The process used a silver iodide plate sensitive to light, which was then developed with mercury fumes and fixed with hot salt water [1]. The process was adopted by the medical community and in 1848, the *Medical Examiner* published the first daguerreotype in dermatological

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literature by Dr. S.P. Hullihen of a burn patient [1]. When heliogravure was introduced in the late nineteenth century, a process that allows for the reproduction of photographs, it became easier to catalog cutaneous manifestations. Dr. George Fox's book in 1880, *Photographic Illustrations of Skin Diseases*, was likely the first dermatology publication using heliogravure [1].

Ever since Daguerre's daguerreotype, photography has become an integral part of dermatological research, most articles today need, if not require, picture supplementation. In the digital world, the array of devices has made the photograph process both more powerful, yet cumbersome for practitioners. Likewise, the various camera and computer software, image file types, and myriad of journals have made it difficult to navigate the journal submission process. This chapter seeks to elucidate dermatology relevant photography, including novel imaging modalities, best practices for high-quality photographs, patient privacy concerns, and the submission process.

11.2 Dermatological Imaging

11.2.1 Digital Cameras

The most common and practical cameras used in clinical practice are Point-and-Shoot (PAS) and Digital Single-Lens Reflex (DSLR) cameras. Notably, the smartphone camera is by far the fastest growing photography tool in both clinical and nonclinical settings; it is indeed a special subtype of PAS, and additional discussion is provided in subsequent sections.

Both PAS and DSLR cameras use the same principles of photography but differ in the image detail/quality, customization/control, cost, size, and learning curve. PAS cameras (Fig. 11.1) are typically easier to use, smaller in size, cheaper in price, less capable of customization, and limited by image quality. While PAS cameras allow some flexibility to change camera settings, most settings are automatically adjusted with each picture. Although inferior to the DSLR camera, recent innovation in the PAS market has significantly improved image quality, and they are effective for most clinical scenarios, with adequate detail for online or print publication.

DSLR cameras (Fig. 11.2) are "professional-grade," large, more complex, and offer the best image quality. The image sensors are typically larger than those in PAS cameras, which allow for greater image resolution. DSLR cameras allow lens interchangeability, offer a wide breadth of pre-capture settings, and provide the photographer with full depth-of-field control (Fig. 11.3). There are also special lenses for close-up and distant images, such as macro lenses and telephoto lenses, respectively. Other settings such as aperture, shutter speed, and zoom are easily modifiable with DSLR cameras. Due to their greater versatility and image quality, they are usually more expensive than PAS cameras.

Fig. 11.1 Advanced point-and-shoot cameras [27]

Fig. 11.2 DSLR camera [28]

11.2.2 Digital Epiluminescence Microscopy

Dermatoscopy, also known as dermoscopy, surface microscopy or epiluminescent microscopy, allows for the visualization of subepidermal morphological features that cannot be seen with the naked eye. It has become almost ubiquitous among dermatologists. In a 2010 survey of US fellows from the American Academy of

Fig. 11.3 Example of depth-of-field control with DSLR camera, creating blurring of the background scene and focus of the foreground scene [29]

Fig. 11.4 Dermatoscope attachment for smart-phone [30]

Dermatology, 46 % of respondents confirmed using a dermatoscope in their practice [2]; in France 94 % of private practice dermatologists use one [3]; and in Australia that number is 98 % [4]. The rise in popularity can be attributed to new research that showed a diagnostic benefit in detecting both pigmented and non-pigmented skin disorders [5–8]. Digital epiluminescence microscopy refers to the digital capture and/or processing of dermatoscopic images via attachment of specialized cameras to a traditional dermatoscope, or directly capturing images onto a specialized digital dermoscopy camera (Fig. 11.4).

11.3 Clinical Photographs

11.3.1 Consent

For standard clinical practice, verbal consent is a minimum prior to photography; and should be documented in the electronic or paper record. Furthermore, written consent is a must if images will be published. Most journals have additional waiver

requirements if images include identifiable information. Some clinics include a photography consent document with initial patient registration forms or as part of the initial permission forms of a research study. In these cases, it is best to include authorization of the physician to use and disclose identifiable images, name of intended publication, purpose for publication, description of images, and patient information [9]. If the patient is an infant, child, minor, or an adult unable to make his or her own medical decisions, then a parent or guardian is required to provide verbal consent or sign forms. Photography in the hospital setting should follow the same consent protocol.

11.3.2 Framing and Site Selection

Careful attention and planning is necessary for patient positioning, draping, and image capture. Isolated lesions, such as an atypical nevus, require at least two photographs: one that captures body location (medium view), and one that captures lesion details (close-up). Generalized skin disorders will require more images, with at least one that is "head to toe" [10]. Attention should be given to minimize surrounding structures such as clothing. For facial photographs, removal of makeup is often overlooked, but an important step to remember [11].

11.3.3 Layout and Background

The best background is a solid color that creates contrast such as black in phototype I–III individuals, or lighter pastel colors in phototype IV–VI individuals. Distracting objects should be eliminated. Some accessories are useful such as tapes and skin markers to illustrate size and highlight areas of focus, respectively. Other acceptable background colors are light blue or green, with minimal light reflection [12]. If space is not limited and serial photographs are expected, constructing a room dedicated to taking photographs is ideal. The background can be permanently installed, instead of reconstructed for each patient, allowing consistency among photographs of different subjects or serial photographs of the same subject illustrating before and after pictures [11].

11.3.4 Distance

The camera to subject distance will depend on the type of lesion being captured. It is usually best to take several photographs with varying distances. For example, a generalized skin disorder will require at least three photographs—a complete

patient view for full extent and distribution, medium distance view for arrangement and configuration, and a close-up image to define morphology of a representative lesion [12].

11.3.5 Zoom

Digital cameras are capable of two types of zoom—optical zoom and digital zoom. Optical zoom refers to the focal length of the lens, which allows similar magnification as physically moving the camera closer to the object. All DSLR cameras are capable of optical zoom, and it depends on dimensions of the lens attached (Fig. 11.5). PAS cameras on the other hand have limited optical zoom. Digital zoom does not increase the size of the real image but stretches out pixels. For example, a camera with 3× digital zoom will stretch each pixel three times its size. This distorts the image and results in poor quality. For this reason, digital zoom should be avoided unless the camera has high resolution.

11.3.6 Macrophotography

Macrophotography allows digital cameras to capture life size images of small objects on digital sensors at a close distance while retaining intricate detail. PAS cameras with autofocus enabled are optimized for long and medium distance stationary pictures, though images captured at a distance of less than 5 cm require the

Fig. 11.5 DSLR lenses with varying ability for optical zoom (largest size allows for greatest zoom) [31]

Fig. 11.6 Camera mode dial. *Red arrow* is pointing to the universal Macro flower icon. Can be used for close-up photos for small lesions such as a single nevus [32]

Fig. 11.7 Macro lens, attaches to DSLR cameras for close-up photographs [33]

macro mode function for optimal outcome (Fig. 11.6). DSLR cameras are also equipped with the macro mode. Additionally, DSLR cameras can use specialized macro lenses for incredibly high-quality macrophotographs (Figs. 11.7 and 11.8). These lenses are expensive, and adequate detail can be captured using either the macro mode on a PAS camera or the standard DSLR lens in macro mode. It should be noted that many smart-phone based cameras do not have macro mode functionality, and in effect close-up images may be more difficult to capture.

Fig. 11.8 Example of a macro photograph using a macro lens with a DSLR camera

11.3.7 Lighting/Flash

Lighting, including flash and ambient light, is one of the greatest, if not the greatest, influences on the final photograph. This is also an area that is commonly overlooked. For example, using a camera's flash too close to the subject can hide characteristic features, due to over exposure. Flash from PAS cameras should be used if there are no other options in a poorly lit room. Natural daylight is the ideal lighting, though this is commonly not practical; a naturally lit room is the next best option. For close-up photographs, ensure the camera is on the macro mode, create ample ambient lighting, do not use flash, and place an appropriate contrasting background [12].

11.3.8 Angles

Similar to lighting, picking the optimal angle will improve photograph quality. Ideally, the image should be taken with the camera's line of sight perpendicular to the skin surface to minimize distortion of the lesions' size and shape [13]. One exception is for short distance shots. In these cases, an oblique angle can capture a clearer image [12]. Also, images taken at an angle to the subject may accentuate the skin contour better than a perpendicular shot, however; this may be problematic if the flash is used [11]. In either case, the patient should not acknowledge the camera or photographer. For anterior images of the subject, it is best to ensure eyesight is directed into the camera. If the view is oblique or lateral, the patient should look at a set item in front of them [14].

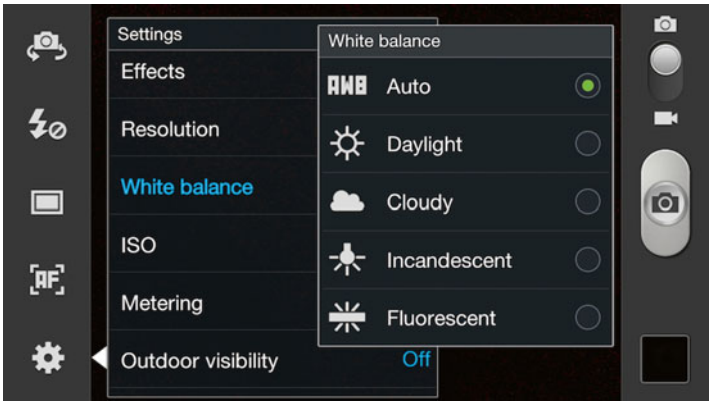

Fig. 11.9 White balance options commonly seen on cameras [34]

11.3.9 Camera Settings

Most digital cameras, especially DSLR cameras, make it easy for users to manually choose camera settings. There are several key settings that clinicians should use and understand to ensure high-quality images: exposure, resolution, focus, white balance, orientation, and macro mode (as mentioned earlier). Exposure is the amount of light to reach the image sensor; it is a factor of the lens aperture and shutter speed. Exposure determines the image depth of field, brightness, and sharpness. The lens aperture controls the size of the lens opening, which determines how far objects in the image remain in focus (Fig. 11.3). Shutter speed controls the amount of time that light is allowed to pass to the image sensor, and determines motion blur. Since most photographs of patients are stationary, optimal settings would include a high aperture and slow shutter speed [11].

Resolution also affects the clarity and detail of an image. A digital image does not always appear the same on a computer screen or in print as it does on the small camera display. The best approach is to capture as much resolution as possible on the camera, and adjust, as needed, in the editing phase. Resolution is sometimes denoted as image size or quality in some camera menus [11]. The highest possible resolution should be used at all times.

Another important feature is focus. Most cameras' autofocus function is suitable for the purpose of taking medical photographs. One useful strategy is to make sure the object is in the focus box; press the shutter-release button midway and wait until the camera confirms the picture is in focus [11]. DSLR cameras allow significant ability to manually focus, and with practice this can add value to image quality. The white balance setting is adjusted based on the type of ambient lighting such as daylight, fluorescent, tungsten, cloudy, and of course auto is always an option (Fig. 11.9).

Typically for photographs taken in patient rooms this setting should be set to fluorescent or tungsten. With practice, a custom preset option can be determined and saved [11].

11.3.10 Microscopes and Slides

Digital cameras can be effectively used with microscopes, and with old kodachrome slides. Microscopic analysis is commonly performed in daily dermatologic care for analysis of hair, Potassium Hydroxide preparations, Tzanck smears, and scabies smears. To capture digital photographs of these highly magnified images, PAS cameras must be used. The camera lens can be placed against the ocular lens of a microscope, and pictures can be taken using the same process described previously. It is best to disable the flash and use the camera's autofocus [15]. A similar technique can be used to digitize old slides. Place the slides on a slide viewbox with background fluorescent lighting and take the pictures without flash. After transferring the images to editing software, crop the image so none of the slide mounts are visible [16].

11.4 Storing Photographs

11.4.1 Image File Types

Choosing an image file type is one of the first decisions when storing pictures. This decision should be made before the photograph is taken as some cameras allow the user to specify initial file type. The three main file types are Joint Photographic Expert Group (JPEG), Raw, and Tagged Image File Format (TIFF). JPEG is usually the default file type on all digital cameras. It is universal across different camera manufacturers but is a "lossy" file type, which means that information is compressed or lost each time the file is edited and saved. Similar pixels are grouped and saved as identical, which decreases the amount of necessary memory [9]. However, most cameras allow JPEG quality to be set prior to taking the photograph. Using the highest quality setting will yield a larger file size and more image information. The JPEG file type is adequate for storage, printing, though not universally accepted among publications.

RAW (or Raw) is not an acronym, and rather it is a noncompressed, or "lossless," format taken directly from the digital sensor with no loss of image information. It is commonly available on DSLR cameras, though uncommon among PAS cameras [12]. Each manufacturer uses a proprietary RAW format. Advanced photographers who want to adjust exposure, white balance or color settings after the picture is taken will have the best ability using the Raw format. This format is not usually accepted for publication.

The other file type option that is "lossless," or does not result in loss of information, is TIFF. A TIFF file is typically much larger than a JPEG, usually five to ten times the memory, but is the highest quality image type and excellent for print. The TIFF format is universally accepted and the preferred storage format.

Whether using a Mac or PC, several editing programs exist that allow image conversion between file types via the "save" or "export" function Also, this software enables lossless compression of TIFFs in order to conserve memory. For instance, Lempel-Ziv-Welch (LZW) compression can result in smaller TIFF files without loss of quality. This can be necessary as some journals place file size restrictions. Therefore, if computer storage space is not limited then it is best to save all image files in TIFF format, with or without LZW compression. However, if space is a concern, JPEG is adequate [12].

To perform more advanced editing such as adding layers, masks, or transparencies to photographs, a Photoshop Document (PSD) in Adobe Photoshop can be created. Depending on the number of adjustments made to the image, PSDs can become large files. PSDs can be readily converted to the more conventional file types such as JPEG or TIFF. Such editing is uncommon, and if necessary, best accomplished by professionals. As a side note, the Graphics Interchange Format (GIF) file type is a popular format for Internet images due to its small file size, though it uses a lossy compression algorithm with limited colors; it is not recommended for dermatologic images.

11.4.2 Cataloging Images

Implementing an organized system for clinical image storage is critical for any research project, and even more important for the active clinician. Fast retrieval is the goal, and upfront planning is essential. One approach is to organize using the operating system native file structure where folders are hierarchically organized by diagnoses (i.e., Windows Explorer or Finder) [14]. Another approach is to use photo editing/organization software, such as Picasa or iPhoto. With the second approach, retrieval is likely faster and visual, though it can be difficult to separate personal and professional images. In either approach, organization by diagnosis should prove useful [14]. To protect patient privacy, avoid naming files with identifying information such as patient name, medical record number or social security number, and instead use descriptions of the lesion or disease. Secure backup to an encrypted external hard drive should happen regularly [12].

11.5 Submitting Photographs to Journals

Most journals now accept manuscript submissions through online websites. Authors can login and provide information such as list of authors, title, abstract, etc. These sites also allow text and graphic files to be uploaded and incorporated into a final

Table 11.1 Image formats accepted by select Dermatology Journals [22–26]

Journal	Formats accepted	Restrictions
J Am Acad Dermatol	JPEG, TIFF, EPS	300 dpi, >5 in. wide, no mention of size
JAMA Dermatol	JPEG, TIFF, PSD, EPS, PDF	300 dpi, >5 in. wide, 800 kB to 5 MB per photograph
J Invest Dermatol	TIFF, PSD, JPEG (not acceptable), EPS (for line art), GIF (accepted but discouraged), BMP (not acceptable)	300 dpi, <1 MB per image, <8 MB total
Cutis	JPEG, TIFF, EPS	300 dpi, no mention of size
Br J Dermatol	TIFF, EPS, BMP	300 dpi, no other restrictions

PAS Point-and-Shoot, *DSLR* Digital Single-Lens Reflex, *JPEG* Joint Photographic Expert Group, *TIFF* Tagged Image File Format, *LZW* Lempel-Ziv-Welch, *PSD* Photoshop Document, *GIF* Graphics Interchange Format, *EPS* Encapsulated Postscript, *ppi* Pixels per inch, *dpi* Dots per inch, *HIPAA* Health Insurance Portability and Accountability Act, *ePHI* Electronic protected health information, *PHI* Protected health information, *GP* Gigapixel photography

manuscript build. Storing images in journal-accepted formats will make the submission process easier; however, not all journals have the same requirements so it is possible images will have to be edited before final submission.

One specification already addressed in a prior section is image file type. Most, if not all journals, accept TIFF images since it is a standard format across all graphic platforms [12]. However, TIFFs are large files and some journals limit memory space for each image. *The Journal of Investigative Dermatology* has a limit of 1 MB per image and 8 MB for all images per article. Therefore, this journal and others including *JAMA Dermatology* and *Pigment Cell and Melanoma Research* recommend or require zip or LZW compression of TIFF images. JPEG images remain a reasonable alternative as they are universally accepted and require less memory than TIFF. Other formats accepted by some but not all journals are Encapsulated Postscript (EPS), Portable Document Format (PDF) and PDS. Photographs inserted into Microsoft Word or PowerPoint files are usually not accepted and should be avoided [10]. Table 11.1 shows a summary of the file types accepted by several of the prevalent dermatology journals.

It is highly probable that both image resolution and size will require editing prior to article submission. Basic graphic software such as Adobe Photoshop or Apple Preview can be used to accomplish these tasks. In these programs, resolution is designated by pixels per inch (ppi), which is sometimes used interchangeably with dots per inch (dpi). The ppi does not change the resolution of images viewed on a computer display as each screen has an intrinsic resolution. Instead, ppi impacts the resolution of print. Most digital cameras save pictures at a default resolution of 72 ppi [12]. The minimum standard resolution for photographs in most journals is 300 ppi. For combination illustrations that have both photographs and text, graphs or line art, higher resolutions up to 1,200 ppi may be required (Table 11.1).

Photo-editing software enables image sizes to be changed with or without altering resolution, depending on the desired outcome. In Apple Preview, image sizing and resampling is available by selecting "Tools" on the control bar and then "Adjust Size." In Adobe Photoshop, the same function is located by selecting "Image" on the control bar and then "Image Size" [10]. Changing the pixel resolution is referred to in these programs as "resampling" the image. Resampling the image will change the number of pixels if the ppi is changed. Conversely, deselecting resample image will simply resize the height and width of the printed image in a proportional scale (i.e., increasing the ppi will decrease the image dimensions and vice versa). Many journals have specifications on image resolution and size rather than resolution alone. In these cases, select resample image, change the resolution to the intended ppi, and manually adjust the picture width. Also, it is wise to use the software's option of proportionally scaling an image width and height unless both dimensions need to be changed.

There are several other items to consider when submitting photographs. All journals require figures, including photographs, to be labeled sequentially as they are presented or referenced in the text. Some journals use numbering formats with either Roman numerals or Arabic numerals. Others might use letter systems but letters are typically used to represent figure parts. All images should be uploaded and labeled individually when submitting online, even figure parts. Legends and captions should be provided separately in a text document. Lastly, any permission to submit copyrighted material, patient photograph consent forms or Institutional Review Board approval forms should also be uploaded in the designated section for submission using the online system.

11.6 Patient Privacy

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 prompted the U.S. Department of Health and Human Services (HHS) to issue two rules commonly referred to as the HIPAA Privacy Rule and HIPAA Security Rule. The HIPAA Privacy Rule protects all identifiable health information. The HIPAA Security Rule complements the Privacy Rule by addressing security standards for electronic protected health information (ePHI) [17]. While it is always important to be cognizant of the Privacy Rule, collecting digital images for research makes the Security Rule relevant as well.

The HIPAA Privacy Rule protects identifiable health information (PHI) stored or used by a "covered entity." Covered entities include health plans, healthcare clearinghouses, and any healthcare provider who transmits ePHI for certain transactions [18]. PHI includes any physical or mental health information, which could reasonably identify an individual including, but not limited to, name, address, birth date, medical record number, or social security number [18]. If PHI is being used in a research study, including a photograph of a person's face or other identifiable

features, it is prudent to seek guidance from an Institutional Review Board or Privacy Board.

The HIPAA Security Rule addresses a subset of the Privacy Rule that deals with ePHI. Generally, the Security Rule requires covered entities to ensure that their workforce protect the integrity of ePHI, anticipate reasonable threats to the confidentiality of ePHI, and do not disclose ePHI without proper authorization [17]. With the passage of the Health Information Technology Act of 2009, all security breaches require notification to patients, HHS, and even the media [19]. Though, it also stipulated that if ePHI is stored and transmitted in an encrypted form, then notification is not required if there is a security breach [19].

Practically, several privacy and security practices should be followed in any clinic where clinical photos are captured. First, a clinicwide manual is necessary to standardize procedures, roles, responsibilities, and proper data management. Get consent of all patients prior to photography; verbal at the minimum and written if plans to publish. Define individual roles to upload, and delete clinical images. Physically secure all cameras, and use password protection when possible. Lastly, this is critical, ensure that images are always encrypted if sent via email; they should never be sent using non-encrypted formats, such as text messaging.

Inset 11.1

The following is an example of a survey on the accuracy in the diagnosis of melanoma. No consent or IRB approval was required. The requirement would have been different if the photographs of the lesions could be identified. As they were nail lesions which could not be attributed to the patients, they were sufficiently anonymous to not require IRB oversight.

Dermatologists at two conferences in 2008 were assessed for their ability to correctly diagnose the cause of melanonychia. Participants included 11 nail experts, 53 senior dermatologists, and 88 junior dermatologists. Diagnostic accuracy for melanoma ranged from 46 to 55 % and was independent of expertise or experience.

Photography devices are now ubiquitous at medical conferences. Often, dermatology conference attendees are warned not to take photographs of clinical images in order to respect and protect patient privacy. As devices become more portable and less obtrusive, these policies will be harder to enforce. It will be up to conference presenters to remove all identifying information from projections.

Di Chiacchio N, Hirata SH, Enokihara MY, Michalany NS, Fabbrocini G, Tosti A. Dermatologists' accuracy in early diagnosis of melanoma of the nail matrix. Arch Dermatol. 2010 Apr;146(4):382–7.

11.7 Recent Advancements in Dermatological Photography

11.7.1 Mobile Devices

With recent advances in compact photography, smartphones have emerged as reasonable alternatives to standalone PAS and DSLR cameras. These devices are now equipped with camera features that rival most PAS cameras. Smartphones are ubiquitous, relatively inexpensive, well known to clinicians, and capable of capturing high-quality images. Many of the devices have third party camera programs ("apps") that can be downloaded and used to take photographs in high-quality JPEG or even TIFF format.

There are several advantages to smartphone cameras, including easy image transfer via wireless Internet or cellular networks, password protection, and remote recovery if lost or stolen. Smartphone attachments are another advantage. Ingraffea described a method of using a dermatoscope connection device that magnifies pictures 30-fold on an iPhone display, which can then be used to capture exceptional digital images [20]. At this time, smartphone cameras are limited by lack of optical zoom, inability to define depth of field, and lack of macro mode, though many images published online and in print are captured on smartphone or tablet devices. Ultimately, as the smartphone camera continues rapid innovation, these devices will become a practical option for most clinical photography within dermatology.

11.7.2 Gigapixel Photography

Gigapixel photography (GP) is a new area of digital photography developed in the last decade, and gaining popularity within various fields. As the name implies, gigapixel photographs capture one billion pixels, which is about 1,000 times greater than current highest resolution cameras. GP was initially used to capture extremely high-quality panoramic landscapes (Fig. 11.10a) and recently extended to the fields of forensic science and pathology [21]. With such high resolution, post image processing allows significant digital zoom and minimal loss of image detail (Fig. 11.10b). The authors of this chapter previously introduced GP's possible applications to clinical dermatology, including more robust total-body imaging for skin cancer surveillance [21]. GP's unmatched photographic detail could also prove beneficial in dermatology research by automating high-definition imaging.

11.8 Main Summary Points

- PAS cameras are typically sufficient to publish high-quality print and online photographs.
- DSLR cameras provide better quality images and more image customization but are typically more expensive and require greater user skill.

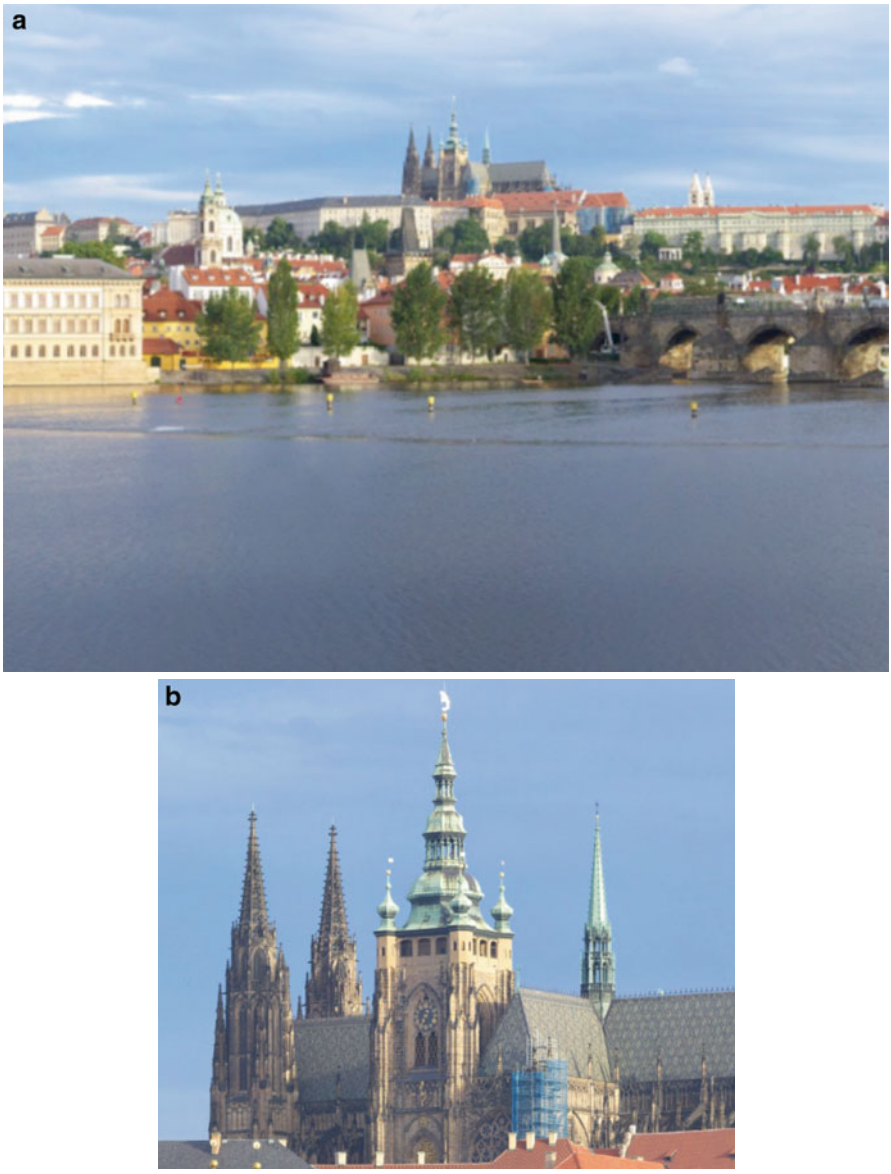

Fig. 11.10 Gigapixel photography—(**a**) full landscape and (**b**) after zooming in on the photo, incredible detail is retained [35]

- Use the macro mode and turn off flash for close-up photography.
- Save images in TIFF format, which is universally accepted by journals.
- Ensure image resolution is at least 300 ppi, a requirement for all journals.
- Implement a privacy policy for photography capture, storage, and management to ensure HIPAA and HITECH compliance.

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Chapter 12
The Regulatory Landscape

Adnan Nasir

12.1 FDA

The FDA is charged with protecting the safety and welfare of human subjects when it comes to clinical trials. The FDA gets its guidance from Congress, which enacts laws that the FDA then implements using rules and regulations. Depending on the circumstances, the FDA publishes rules, repeals, or amendments in the Federal Register pertaining to the most current legislation. The FDA allows a public comment period for feedback on a proposed rule. The FDA may publish a preamble to regulations which include public comments by interested parties and the FDA's response to them in formulating its final ruling. In its response, the FDA may agree with or reject public comments and act accordingly in developing its regulation.

The FDA has been political since 1988. Commissioner appointment required Senate confirmation. Commissioner turnover has been an issue at the agency. Politics add uncertainty to the regulatory process at the FDA. In recent administrations, there has been:

- Increasing infusion of religious doctrine and implementation of ideology rather than data-driven public policy
- Censorship of science-based information
- Removal of medically important data from healthcare web sites (for example, data showing the efficacy of condoms in preventing HIV and STDs were removed from the CDC web site)

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- Politically motivated shift in resource allocation
  - In the 1990s, HIV prevention programs lost $4 million
  - During the same period, abstinence-only program budgets went from $20 million to $167 million despite evidence showing a lack of effectiveness

These politically driven changes affected patient education, standards of medical care, the selection of research topics, grant writing and review, and the research funding process. In 2004, Elizabeth Blackburn was dismissed from the President's Council on Bioethics. She won the 2009 Nobel Prize in Medicine.

The FDA rules regarding good clinical practices (GCPs) in clinical trials fill several sections of the Federal Register. Parts 50 and 56 govern informed consent, institutional review boards, protection of human subjects, protection of children, and exceptions to informed consent. Part 54 discusses principal investigator financial disclosure. Part 210 regulates pharmaceutical good manufacturing practices (GMPs) and investigational new drugs (INDs). The FDA has additional standards for antibiotics, biologics, and vaccines. Parts 312 and 314 discuss new antibiotics, biologics, clinical hold for life-threatening conditions, and disqualification of a clinical investigator. Part 320 includes sample retention rules and requirements for bioequivalence studies. Part 812 covers use of investigational devices. Part 814 covers medical devices and humanitarian uses of medical devices. A Miscellaneous section has a Part 11 which covers electronic signatures and electronic records, information systems such as the Bioresearch Monitoring Information System (BMIS), and the presiding officer.

Inset 12.1

Sec. 50.25 Elements of informed consent.

(a) *Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Source: Code of Federal Regulations: 21CFR50.25

Informed consent regulations are in Part 50. The scope of the rule covers all clinical investigations including foods and dietary supplements bearing a health claim, infant formulas, food additives, drugs, medical devices, biological products, and electronic products. Part 50 also covers informed consent, which has basic elements and additional elements. The additional elements include: unforeseeable risks to the subject, or, as applicable, the subject's fetus or embryo; whether and how the investigator may terminate the study without the subject's consent; additional costs for which the subject may be responsible during the course of the study (for example, transportation to the clinic, or parking on at the research facility, copying, and mailing study-related medical records); the consequences of withdrawing from the research protocol (for example, possible rebound of skin disease if a study drug is abruptly discontinued), and the procedures for withdrawal; a statement that new findings related to the study drug may be made available to the subject as they become known (for example, if a drug is vastly superior to placebo in a melanoma trial, the trial may be halted as further delivery of placebo may be considered unethical; and the approximate number of subjects in a study. The informed consent will also contain the following statement, as required by law:

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

In the case of studies involving children, no additional IRB requirements are necessary as long as the risks to children are minimal, and adequate provisions are made for soliciting the child's assent and the parent or guardian's consent. If the risk to children is greater than minimal, the IRB can only approve a study if the (a) the benefits justify the risks, (b) the benefit is at least as great as that offered by already available alternatives, and (c) adequate provisions are made for soliciting the child's assent and the parent or guardian's consent. In studies where the risk is greater than minimal, and no direct benefit to the volunteer is provided other than providing generalizable knowledge, the IRB must show that the added risk is only a small increment above minimal risk and that the knowledge obtained is vital for improving or understanding the subject's condition. For conditions not meeting the above criteria, but which the IRB or sponsor feel merit consideration for study, the petition must demonstrate that the study offers (a) a reasonable potential of understanding or improving a serious condition which affects the health or welfare of children, (b) the Commissioner of Food and Drugs consults with a panel comprised of appropriate experts (for example law, medicine, education, ethics, science) and allows a period of public commentary which confirms the sponsor's stance, and which is conducted according to solid ethical principles.

12.2 Audits

Audits are common, and even more common if you are a successful investigator with a successful study. Often, the FDA will audit sites which are 'high enrollers' in studies. One of the best ways to be ready for an FDA audit or inspection is to be

prepared. You will get little notice, typically 1 week, to get ready, and unless you are away because of illness or a long-planned vacation, accept the appointment day granted by the agency. Delaying the inspection will be granted, but, unless it's for a good reason, is likely to earn you even more scrutiny.

Preparation for audits begins long before they ever occur. As an investigator or research site, you and your staff need to understand the requirements of the FDA for studies. You need to make sure you have all of your documentation in order. You need to have internal policies and procedures for ensuring the quality, integrity, and validity of your data, and the health, welfare, and safety of your research subjects. You need to make sure your protocols are carefully followed, and that any deviations or violations are carefully documented, and addressed. You need to take advantage of your sponsor oversight to ensure that you are following the protocol. You need to listen to your monitor during your studies. You also need to make sure your training and certifications are valid and up-to-date. As part of your training, you may wish to hold periodic mock-FDA audits to prepare yourself and your staff.

When you learn of an audit, notify your sponsor immediately. Some sponsor agreements require it, and some sponsors have the resources to help you deal with the administrative burdens of an audit. It is in the sponsor's best interest to have you emerge successfully from an audit so that the data you have worked so hard to deliver, and they have paid so much to collect, remains valid and usable in a drug or device application.

You also should get familiar with FDA procedures, so that you can be prepared for the types of questions, and inquiries you will face. It will give you confidence during the visit to address any scenario that might arise. Plan on getting an experienced, thorough, and poker-faced agency officer visiting your site. This will ensure that you are overprepared.

The results of audits can be hard to predict, and factor in many possibilities, including sidelines of inquiry by a curious agency inspector and fishing expeditions if you or your staff get off tangent. This should not happen if you are prepared and answer only the questions you are asked. However, it is good to have someone taking notes while the auditor is at your site. The notes should include dialogue, and observations on what the inspector is doing and where he or she is going. This way, you will be able to corroborate or challenge the details of any finding or report submitted by the agency. A good note taker is someone familiar with audits and the policies and procedures of clinical trials in general and your site in particular.

Have one person designated to be assigned to the auditor. This person should be the primary contact for the auditor and escort him or her throughout your facility.

Some of the documents you will need for the auditor include an information brochure about your organization, including an overview of your research site, an organizational chart, and any complaints about your site. Have all your documents ready, and be sure that your facility is in top shape for inspection.

It is good to prepare your staff for questions the auditor might ask. Questions typically revolve around company policies, the job description of each employee including their duties, training, and qualifications. There may be questions about errors, and policies and procedures for handling errors. Be sure your staff knows

how to answer these questions with the most current and accurate information. If they don't know an answer, be sure they admit it, and offer to research answers and get back to the inspector as soon as possible.

Be sure your most diligent staff are around on the day of the inspection. The auditor may not speak with everyone, but will likely be observing the activities and processes of your facility during the course of the inspection. If feasible, problem workers and inexperienced workers should not be on duty on the day of the inspection.

Auditors want to make sure that your study was done according to the protocol and FDA guidelines. They have a checklist that they go through. Knowing this checklist will help you prepare for an inspection.

1. They want to be certain that the data are of high quality, valid, and collected properly.
2. They want to make sure human subjects were protected.
3. They want to know that the sponsor, CRO, PI, and site adhered to all regulations, guidelines, GCPs and the final version of the IRB approved protocol.
4. Types of audits:

    a. Audits can be for bioequivalence studies, where only one study is the basis for approving an equivalent pharmaceutical.
    b. Routine audits are typically for studies such as primary efficacy studies, and studies submitted for marketing, licenses, or NDAs.
    c. For cause audits, because there is a concern expressed about a particular investigator.

Study-related audits typically involve randomly selected study sites. Occasionally sites that meet certain criteria are selected as well. These can include sites which have high enrollment, sites which enroll subjects very rapidly, sites which conduct numerous studies simultaneously, sites which conduct pivotal trials on which the majority of the IP's claims are based, and sites which switch a pharmaceutical or device from prescription to OTC status. Many times, sponsors can predict if your site is likely to be audited.

For cause inspections occur under a number of circumstances. An investigator may be selected for inspection if he or she conducts many studies outside his or her specialty. If an investigator conducts a pivotal study for NDA or a license, he or she may be audited. If the investigator submits safety and efficacy data which depart significantly from other sites under the IND/IDE, there may be an inspection. If the sponsor notifies the FDA or the subject complains to the FDA, the site may be investigated. If a study garners a lot of extra media attention, it may be audited. If there is a larger number of subjects than would be predicted with a specific diagnosis, an audit may be triggered. For example, if you are doing a study of a rare genodermatosis, and are in a small town, and recruit several-fold more subjects for your study than sites in large metropolitan areas, you may be subject to an investigator-related audit.

You will be notified, and your sponsor will be notified in writing with a Notice of Inspection on FDA Form 482. The agency will request a meeting at a reasonable time that is mutually convenient. You are typically given a few days to a few weeks advance

notice. Respect the agency's time frame. If you delay more than ten days without a very good cause, you will only raise suspicion and more intense scrutiny. The FDA may request an audit any time, even many years after a study has been completed. Neither you nor your sponsor may legally refuse access to your files to the FDA.

As soon as you become aware of an FDA audit, notify your sponsor and the IRB. The FDA may also inspect the IRB related to the study if it has not been inspected in the past 5 years. Depending on the complexity of the study, the size of your site, and other factors, an audit may last 3–5 days.

As an investigator, familiarize yourself with the study. Review the protocol in detail, including the consent, inclusion and exclusion criteria. Review the data, including protocol deviations and violations, adverse events, and any situation where there was a complaint, or an issue regarding the health, safety or welfare of subjects. Review your SOPs and be sure you followed SOPs and GCPs in addressing any concern and that you documented your findings and any corrective actions clearly and thoroughly.

Be familiar with your staff and the staff who worked on the study. Some of the staff may have left or retired, particularly if the audit occurs years after a study closeout. Review your study documents and make sure they are all readily accessible, organized, and complete. As you review the documents, ask if they verify drug or device accountability, and compliance with regulations (including an updated FDA 1571/1572, IRB review and IRB approval, IND safety reports, current Investigator's Brochure, current Protocol, financial disclosures, and all communication with the sponsor and the FDA). Be sure that you and your staff have the proper documents certifying your credentials (medical licensure, CLIA licensure, DEA licensure, in-house training, CVs current over the past 2 years, and any additional training—for example, GCP training, CITI training). Other important study documents which show protocol compliance are legible and accurate CRFs and source documents. Be sure these documents explain any deviations or violations, any adverse or unanticipated events, and any appropriate follow-up.

Inspectors use these documents to verify the existence of subjects, their eligibility for enrollment (through source documents like medical records, clinic visit notes, shadow charts, lab results, imaging results, prescriptions, signed informed consent). Inspectors want to verify that the informed consent was gathered according to regulations and was signed before participation in the study.

You should have at hand all the documents the inspector needs. However, you should ask the inspector what documents they require. Each site, inspector, and case is different. They will know if they are there to address only specific questions or do a more comprehensive inspection. The FDA follows a guidance manual which is available online. You can read it to see the inspector's checklist: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm.

Set aside a space for the inspector that is comfortable, clean, and free of distraction. Do not offer amenities such as coffee, donuts, lunch or anything that could be misconstrued as unduly influencing the inspector. Take documents to this area as they are requested by the inspector. Be sure that you and your staff are available if called by the inspector. Do not leave the inspector unaccompanied. Be sure the inspector has access to a photocopy machine.

When inspectors arrive, they formally display their credentials, and present you with FDA Form 482. They will interview you, and your staff. Be sure you and your staff answer questions clearly, politely, and honestly. Answer the questions that are asked, but do not offer additional information or go off on tangents. If you don't know the answer, or can't recall, say so immediately. Offer to look up the answer, or research the answer and get back to the inspector if that is something you can do.

At the end of the audit, the inspector has an exit interview with you to discuss findings and get answer(s) to any question(s). Some auditors will let you know right away if there are any findings or deficiencies and if a FDA Form 483 will be filed or not. Other auditors will let you know that they are returning to their headquarters and will send you a report of their findings in writing at a later date.

The inspector may note the following in the report:

1. No action indicated (NAI), which means your site is in compliance and in good standing. This type of finding does not require a response, although an acknowledgement is respectful.
2. Voluntary action indicated (VAI), means the auditor has found problems, but of a minor nature, which do not affect the health, safety, or welfare of subjects and do not affect the quality or integrity of the data. You will receive the details of a VAI in writing and will need to respond.
3. Official action indicated (OAI), means that a serious problem has been discovered, one which will likely result in some sort of sanction, and require a response from the investigator and/or sponsor and may lead to a reinspection to make sure all concerns have been addressed.

If you do get a deficiency letter, you are required to respond to it. If your response is considered satisfactory, the deficiencies will be removed from the Form 483, and not part of the Establishment Inspection Report (EIR). So it is to your benefit to thoroughly research any concerns your inspector has and address them to the FDA's satisfaction.

You may get a warning letter if you do not properly respond to the EIR, or if you or your site has substantial deficiencies. You must respond to warning letters within 15 days, with a clear corrective action plan. If you do not adequately respond to or comply with the contents of a warning letter, you could be disqualified from conducting trials, disbarred, or prosecuted.

12.3 Overseas Trials

From a regulatory standpoint, it is difficult to monitor overseas investigative sites and IRBs. Some countries are not amenable to FDA oversight because of distance, legal limitations, or lack of FDA staff and financial resources. Overseas sites may have fewer local resources to monitor the quality of studies. For example, the Drugs Controller General of India has three pharmacists and no physicians on staff. In 2013, following an inspection which demonstrated "significant cGMP (current good manufacturing practice) violations," the FDA banned the importation of generic products manufactured in four Ranbaxy facilities in India.

Climate, in a 2009 review in the *New England Journal of Medicine* [(26):816–823] examined the migration of trials overseas. Contrary to public perception, and the impression of most US-based investigators, the FDA does not require studies of drugs marketed in the United States to be done in the United States. In the past, the FDA required foreign research to be done under ICH or Declaration of Helsinki standards. In 2008, the Helsinki standard was abandoned by the United States.

Countries have different levels of attractiveness based on patient pool, cost efficiency, regulatory climate, expertise, and infrastructure. This was studied by A. T. Kearney (Bailey et al. Make Your Move: Taking Clinical Trials to the Best Location, Pharmafocusasia.com). They ranked China a close second, however, recently, it has fallen into disrepute for data fabrication and bribery.

12.4 Drivers of Overseas Growth

With compliance voluntary, with lax oversight abroad, and with minimal or no enforcement of regulations and guidelines in US courts, pharmaceutical companies have little incentive to protect human subjects abroad. There has been an enormous shift in fulcrum of clinical trials from the United States to the rest of the world (Fig. 12.1). With cost being a principal force driving research abroad, and with additional financial savings from not complying with all the guidelines and

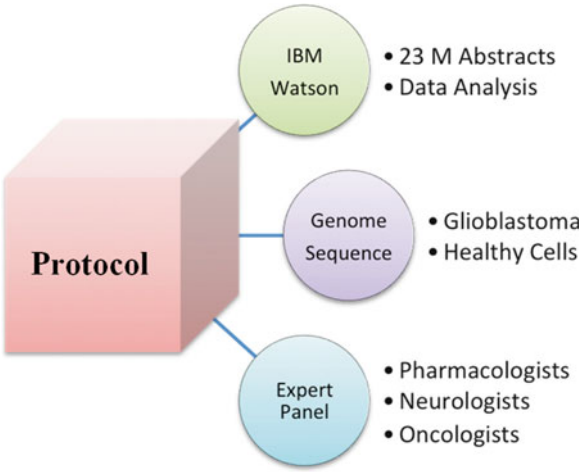

Fig. 12.1 Clinical trials involving big data will utilize massive input of genomic data on volunteer tissues and data from the scientific literature to conduct pilot studies of therapies in small subsets of patients. One trial of glioblastoma involves twenty patients. They will have two genomes –that of their healthy cells, and that of their tumor biopsies—fully sequenced. The data will be entered into IBM's Watson and compared with Watson's enormous database of abstracts from the scientific literature to search for applicable therapies based on the volunteers' genomes. Watson will then suggest therapies for review by an expert panel. Those deemed feasible for clinical evaluation will be implemented and studied for outcomes.

regulations surrounding human subjects research, pharmaceutical companies have enormous financial incentives to continue promoting research outside the United States.

- Access to patients.
- In Asia, Wyeth has identified Phase II Super Centers (9,000 outpatient visits/day; Patrick McGee "Clinical Trials on the Move").
- There are overseas hospitals specializing in diseases (heart disease, diabetes, etc.).
- Many overseas patients are treatment naïve.
- Efforts are needed to test medications in different ethnic groups (Iressa is effective in Asia, but not in United States). Japanese in Brazil are a key study group.
- Approved doses vary by country (Japanese doses tend to be lower in 1/3 of cases).
- ADRs differ among ethnic groups.
- Slow recruitment causes 85–90 % of the delay and is costly.
- Recruitment rates are higher, and costs are cheaper abroad.
- Local clinical trials also groom markets and grease wheels in developing countries seeking status and recognition.

Some US insurance plans prohibit member participation in clinical trials. HIPAA makes recruitment difficult. The standard of care in the United States is high which competes with clinical trials. In the third world, participation in a clinical trial may lead to treatment far superior to the local standard of care. As the uninsured population in the United States grows, these trends may not continue unabated.

12.5 Drawbacks to Overseas Growth

- Little information on foreign IRBs
- Difficult to audit foreign PIs
- Patient understanding and education may vary
- This calls into question adequacy of informed consent and level of volunteerism in participating

The Declaration of Helsinki was revised in 2008 to increase transparency and safety for subjects. It required investigators to disclose conflicts of interest to IRBs and study subjects, to publish negative study findings, and to register trials in a public database before enrolling subjects. It also discouraged the use of placebos unless there was no other treatment alternative, or giving a placebo caused subjects harm. The Declaration of Helsinki is subject to the governance of the World Medical Association, which is outside the control of the FDA. The agency decided in 2008 to drop the requirement to comply with the Declaration of Helsinki. Instead, it required compliance with the ICH GCP guidelines. The latter is not an ethical code. It is a regulatory procedural document. It does not aspire to high values of ethically responsible research.

12.6 The Challenges of Doing Studies Overseas Include the Following

- Lack of a skilled workforce. There is a shortage of mentors, of qualified academic staff, inadequate academic infrastructure, and a flight of well-educated well-qualified workers to developed countries. The number of physicians in Rwanda per 1,000 is 0.02, while that number is 3.58 in Sweden.
- Trend away from medical school. Applications to medical school in developing countries are down over the past 20 years.
- Lack of infrastructure. Whether referring to teaching and research opportunities or civil unrest or unpredictable electricity or inadequate roads, many factors conspire against a stable clinical research workforce.
- Diversion. Studies sponsored by multinational corporations drain already thin resources and recruit what few clinicians and scientists who are in country away from pressing social needs to high status jobs in gleaming privately funded laboratories.
- Respect. Investigators in developing nations complain that their work is not recognized by grant agencies or scientific journals and is often rejected or neglected. This erodes morale.
- Cost. Maintaining and supplying a modern laboratory in a country with limited transport, limited clean water, inadequate sewage, and inadequate power requires costly importation and repair. Often, if equipment breaks down, it is not repaired because shipping parts from overseas becomes too cumbersome.
- Strife. Whether political unrest, war, or natural calamity, resources from health care are often stretched thin, treating war casualties, victims of epidemics or famine, or victims of natural disasters.
- Attitudes. Cultural and social beliefs combined with varying levels of basic education may alter participation rates or approval mechanisms for clinical trials. There may also be suspicions of caregivers of a different ethnic background than the population being studied.
- Ethics. Poor populations in developing countries are particularly vulnerable to coercion or inducement. The ethical requirements of IRBs vary among nations.

Many US companies are shifting trials overseas because they are cheaper, and pools of subjects are larger.

Issues raised include uniformity of standards and regulatory issues.

Race, justice, and economics also come into play. Vulnerable populations share:

- Limited economic development
- Inadequate protection of human rights
- Inadequate community and cultural experience with, or understanding of, scientific research
- Limited availability of health care and treatment options
- Limited ability of individuals to provide informed consent due to literacy, language, educational, or cultural barriers

Inset 12.2

Vulnerable Population

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.

Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention.

Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless perons, nomads, refugees, minors, and those incapable of giving consent.

Harvard received millions of dollars of grants for studying the DNA of Anhui people, who were promised health care which never materialized. Volunteer rates there exceeded 95 %, perhaps due to local party official coercion. The US Embassy in Beijing warned US medical researchers from working in poor areas of China where people are poor, health care is poor, and people are unable to protect their rights.

Inset 12.3

Overseas Trials

Countries outside the United States where clinical trials are conducted may have limited economic development, making financial incentives for investigators and subjects more prone to triggering conflicts of interest. There may be insufficient protection of or oversight of human rights. There may be cultural concern barriers to clinical research. For example, in native New Zealanders, informed consent requires approval of the entire community, not just the subject or volunteer. The limited availability of clinical care options in emerging economies may give the trial monopoly status as a healthcare provider.

In one gene sequencing study in rural TuoTuo China, subjects were told they would be provided with free health care in exchange for their participation. In reality, they were provided with none of the promised lab tests, clinical screenings, follow-up evaluations or discounts on healthcare visits. Furthermore, few of the funds distributed for the study reached the subjects. Volunteers were also forcibly made to participate under pressure of local government officials.

John Pomfret & Deborah Nelson, The Body Hunters: Harvesting China's Blood; An Isolated Region's Genetic Mother Lode; Harvard-Led Study Mined DNA Riches; Some Say Donors' Promises Were Broken, WASH. POST, December 20, 2000, at A1.

Nigerian children were studied by Pfizer for a quinolone (Trovan) for meningitis. In the study, an oral drug was given, no monitoring of progress with spinal taps was done, and no rescue medication was given if patients were worsening, and the dose was 1/3 of the dose given in US trials. In 2009, a federal appeals court ruled that Nigerian families could sue Pfizer in US courts, this is pending before the US Supreme Court. In Nigeria, officials sought $9 billion in criminal charges against Pfizer, and settled in July 2009 for $75 million.

In 1996, there was an epidemic of bacterial meningitis in Kano Nigeria, a region already suffering from epidemics of cholera and measles. The antibiotic Trovan (a quinolone class member), developed at the time, could not be studied in children in the United States, because it was known to cause chondrodysplasia, arthropathy, hepatocellular damage. A drug company physician saw the outbreak as an opportunity to test the medication on children and sent a six-member team to Kano.

He obtained FDA approval to export the drug by getting the Kano government approval, and a Nigerian hospital's ethics committee's approval. At the time, there was no formal review process, and there were no uniform guidelines for human subjects research in Nigeria. The team arrived at Kano's Infectious Disease Hospital and began treating children with meningitis with either a full dose of oral Trovan, or a partial dose of intramuscular ceftriaxone. Subjects were never informed that they were part of a clinical trial. They were never told that already-proven effective treatment was being provided for free by other clinicians in the same hospital. Subjects did not get all the laboratory tests required by the trial. After 2 weeks, members of the team left, and told subjects to follow-up with other clinicians at the hospital. Of the 198 children studied, 11 died, 5 in the Trovan arm, and 6 in the ceftriaxone arm. Around 60 children in the trovan developed arthralgias. After the trials, the company applied for FDA approval of Trovan for pediatric meningitis. Only after an audit of the study documents from Nigeria did the company withdraw its application for epidemic meningitis. The drug company was sued in the United States and the lawsuit underwent an appeal process with outcomes not favorable to the plaintiff.

"Statistics are people with the tears wiped away." Dr. Irving Selikoff One Hungarian researcher remarked patients in the United States have an overdeveloped sense of their rights and fear of being harmed. It helps to understand the local culture. In some parts of Kenya and Nigeria, researchers are not welcome to ask about subject's personal habits. Revealing homosexuality can be dangerous, making one vulnerable to attacks or death. Sensitivity to the norms of a society can go a long way toward successfully engaging study participants.

Strengthening local IRBs ensures institutional transparency and rigor in the trial design and approval process. This can be augmented by training investigators in developed nations before they return home. It can be done in person and reinforced online.

Provide additional health care. Communities that benefit from overall healthcare delivery as a bonus for participating in clinical trials may be more committed to participation.

Technology, whether online resources, or solar power, can help maintain and sustain a clinical research enterprise.

The long view. Study projects that have a long-term plan tend to reinforce community ties. Studies that are short-term interventional studies are best incorporated into an existing healthcare setting so that continuity of care can be maintained at the end of the study.

12.7 Gap Trials

The international conference on harmonization (ICH) was formed to establish international guidelines for human subjects research. They are published in the Federal Register, but do not have the force of law in the United States or abroad. The guidelines, as they are, are strictly voluntary. The DHHS and FDA require that human subjects research done in the United States and abroad should comply with US

regulations. However, these requirements only apply to federally funded research, and to research on drugs and devices specifically regulated by the FDA. 'Gap Trials,' those that do not fall into either category (for example, privately funded research, research on surgical procedures and techniques, and behavior therapy research) or the so-called Common Rule are not currently subject to US law.

Inset 12.4

Gap Trials

A systematic review of around 24,000 clinical trials was conducted in 2014. This revealed that 5–16 % of clinical trials in the United States don't fit into categories covered by federal regulations such as the FDA's human subjects protections or the Common Rule. Half of the studied trials were covered by the FDA's rules, 10 % by the Common Rule, and another 25 % by both rules. This left around 15 % which were not covered by federal regulations falling into the so-called "gap." Gap trials may still have ethical and patient safety backups in place. Gap trials may include nonfederally funded research. In the past two decades, bans on federal funding stem cell research have led to private sources of funding for stem cell and reproductive technologies. Some experimental surgical techniques which are not federally funded fall into the gap. Despite existence outside of federal policy protections, gap trials may still be regulated. For example, many institutions require that all trials, whether they are gap trials or federally covered trials follow the same ethical guidelines.

Zarin DA, Tse T, Menikoff J. Federal Human Research Oversight of Clinical Trials in the United States. *JAMA*. 2014;311(9):960–961.

Lowe NJ, Lowe PL, St Clair Roberts J. A phase IIa open-label dose-escalation pilot study using allogeneic human dermal fibroblasts for nasolabial folds. Dermatol Surg. 2010 Oct;36(10):1578–85.

12.8 Innovative Trials

In 2006 FDA tried to boost drug development w/new guidelines. They are streamlining a path called the Critical Path Initiative. This was in response to an agency publication which looked at the reasons behind stagnation in clinical trials. A Critical Path Opportunities List was created to look at specific areas where product development had the greatest need. It detailed 76 examples where new advances in genomics, imaging, and data analytics could be used to pave the way toward new discoveries in the diagnosis, treatment, and management of critical diseases such as diabetes, Alzheimer's disease, and cancer. Critical Path Initiatives include adaptive

design clinical trials for drugs and biologics, non-inferiority clinical trials, and trials using surrogate markers of disease such as biomarkers for tuberculosis.

Exploratory IND studies:

- Phase 0 or microdosing trials
- Less than 1/100 (up to 100 mcg) of expected dose is given
- Only 8–10 volunteers
- PK and PD can be studied with advanced assays and imaging techniques
- Especially handy for cancer studies
- Can be used to develop biomarker assays
- Guidelines provided by NCI
- Example is Abbott's ABT-888 tested in 14 volunteers, data analysis to POC in 6 months

12.9 Rare Diseases

In 2009 FDA launched TRND (Therapeutics for Rare and Neglected Diseases) program.

- Program bears financial burden of preclinical work.
- If successful, it pairs with private industry to test in patients.

The FDA defines rare diseases as those affecting fewer than 200,000 people. These diseases tend to be genetic and many begin in childhood or infancy. Dermatologic examples include genetic bullous dermatoses, xeroderma pigmentosum, and pachyonychia congenita.

Section 740 of the Appropriations Act of 2010 empowers the Rare Diseases Group (RDG) to evaluate products including devices, drugs, and biologic agents for the prevention, diagnosis, and management of rare diseases. The RDG anticipated an influx of new therapies for rare diseases because of a convergence of modern technologies such as: genomics, proteomics, bioengineering, targeted therapeutics, nanotechnology and informatics.

Based on FDA review of the RDG findings, the agency made the following regulatory provisions: fast track and accelerated approval processes for new drugs and devices for life-threatening conditions; priority review for products used to treat serious diseases; priority review for products used to treat less serious diseases which offer a significant advance over existing treatments; expanding access to patients for investigational products.

The agency identified key areas of focus in this initiative. These include increasing the fund of knowledge of rare diseases by: gathering natural history data and generating databases; identifying and ushering the maturation of quality biomarkers (such as molecules, or other biological factors in blood, body fluids, or tissues); and using novel clinical trial designs and statistical methods suitable for rare disease development programs.

The agency recommended increased collaboration inside and outside the FDA to establish a standardized method to identify suitable biomarkers. This initiative is called the Biomarker Qualification Process. The FDA is also encouraged to participate in conferences and consortia along with investigators to offer guidance in developing diagnostics and therapeutics for rare diseases.

The FDA is using surrogate markers to measure efficacy, i.e., HIV drop in viral load or increase in CD4. Imaging such as PET or serum PSA can be used to monitor early response to cancer therapy. Sometimes surrogate trials have problems. For example, rosiglitazone (Avandia) was shown to effectively lower blood sugar, an effective surrogate marker for diabetes control, but it increased the risk of myocardial adverse events. Also, improving surrogate markers such as lower prostate specific antigen (PSA) level may not improve overall survival or quality of life, especially for cancer drugs. Agalsidase beta (Fabrazyme) was approved for the treatment of Fabry's Disease through an Accelerated Approval process based on the results of a single study and the drug's effects on a single surrogate endpoint.

12.10 Neglected Tropical Diseases

Partnerships being formed for the study of neglected tropical diseases are getting funding from pharmaceutical companies, the Gates Foundation, and the NIH. These have led to the development of projects for the treatment of several infectious diseases with dermatologic manifestations including leishmaniasis, filariasis, Chaga's disease, schistosomiasis, and viral illnesses such as dengue fever. The World Health Organization is creating fellowships for young researchers from developing countries to get trained with established investigators, and return to their native homeland to conduct clinical research and to train their fellow citizens.

Neglected Tropical Diseases affect a significant subset of the world's population. These include: tuberculosis, malaria, trachoma, buruli ulcer, cholera, dengue hemorrhaticc fever, dracunculiasis, fascioliasis, trypanosomiasis, leishmaniasis, leprosy, filariasis, onchocerciasis, schistosomiasis, helminthiasis, and yaws. There are currently no FDA approved drugs for Buruli ulcer, dengue fever, dracunculiasis, and fascioliasis. Nanoparticulate liposomal amphotericin B is FDA-approved for leishmaniasis. There are no FDA-approved diagnostic tests for Buruli ulcer, dracunculiasis, fascioliasis, trypanosomiasis, leprosy, filariasis, onchocerciasis, or helminthiasis. While there are experimental vaccines for tuberculosis, malaria, and dengue fever, there are no FDA-approved vaccines for any of the other neglected tropical diseases.

The Neglected Tropical Disease Group reported that most such diseases occur in tropical climates, and are transmitted by insects, contaminated water, or contaminated food, and tend to be endemic in areas of poor hygiene and sanitation. The agency noted that sanitation and mosquito repellant bed net play a significant non-pharmacological role in preventing neglected tropical diseases. The NTD Group recommended guidance for development of drugs for the treatment NTDs, CDRH

expert panels to discuss the regulation of tests for the diagnosis of pulmonary tuberculosis, the treatment of pulmonary tuberculosis, and the use of combination therapies. The NTD Group recommended revised guidelines for CBER for the development of vaccines against global infectious diseases. A recommendation was made to consider Orphan Drug Grants be accessible to studies of diagnostic and therapeutic modalities for NTDs.

12.11 Information Science

One example of the power of informatics is the exploitation of powerful computers to assist in the design and implementation of clinical trials. Oncologists are currently creating drug cocktails to address genetic mutations in cancer to tailor individualized therapies. Simply knowing the genomic composition of a cancer is not sufficient to formulate a therapeutic regimen. Many mutations discovered in a cancer may be irrelevant or incidental to its survival. Only a few key mutations may be drivers of a cancer or weak points to attack with drug or drug/device combinations.

The premise of bioinformatics is that the body of literature exploring genetic mutations and vulnerabilities in biology, and especially cancer biology, is growing at too rapid a rate for any one individual, or group of individuals studying cancer to digest and exploit. This creates a scientific bottleneck, where a critical clue or answer to cancer therapy may be 'out there' but inaccessible to or underappreciated by a cancer treatment group.

Deep knowledge-based computers and algorithms such as IBM's Watson have been able to store and exploit vast sums of information and use them to answer questions and solve problems such as chess games and quiz show games against formidable human champions. The Watson system is now reviewing and storing the cancer literature found in Medline. It has stored and catalogued 23 million abstracts to date. The system is being used to design a clinical trial.

In a pilot study of glioblastoma, 20 patients will have their two genomes—that of their healthy cells, and that of their tumor biopsies—fully sequenced. The data will be entered into Watson for analysis. Watson will look for discrepancies, and identify mutations which, based on its review of the literature, are specific to the tumor, and relevant vulnerabilities for therapeutic intervention. It will then generate a list of recommended treatment protocols. This type of data analysis can occur in seconds. The recommendations will be made available to an expert panel of pharmacologists, oncologists, and neurologists for assessment of feasibility and quality of the data being reviewed. If the system proves effective, the database may be expanded to include entire journal articles rather than simply abstracts (Fig. 12.1).

From humble beginnings, the FDA has gone from a small federal agency to a large multifaceted government enterprise with global reach. It has coped up with upheavals in politics, hamstrung leadership, and fickle financial resources to complete its mission. It has adapted to industry pressure, public clamor, epidemics, new diseases, and falling borders to keep patients, and patient safety as its focus.

Chapter 13
Industry

Adnan Nasir

13.1 Industry Perspective

It takes 12–15 years for a new drug to be brought to market. Some medications, such as those for AIDS and cancer have a fast track pathway. In 1992, the Prescription Drug User Fee Act passed, and time to clinical testing and approval went from 9.2 to 6.9 years. Newer biopharmaceuticals (monoclonal antibodies, biologics, cytokines) require more time, leading the average to go up to 8.5 years. Only 1/1,000 drugs make it from animal testing to human trials. Only 1/5 to 1/10 at this stage get final marketing approval from the FDA for use in humans. The gap between pre-clinical studies and clinical approval is very expensive [1–4]. The costs and risks at this juncture often bankrupt sponsors and venture capitalists. Uncertainties in the return on investment (ROI) of a new compound or its ability to get to market before a competitor lead many sponsors to abandon otherwise promising projects. This expensive, risky, and high rate of failure phase is called the Valley of Death (Fig. 13.1). Only 3/10 approved drugs recoup development costs. The typical cost breakdown for a clinical trial is as follows:

- Investigator $150–200 million
- CRO $50–100 million
- Central labs $10–15 million
- Monitors $8–12 million

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DOI 10.1007/978-3-319-09027-6_13

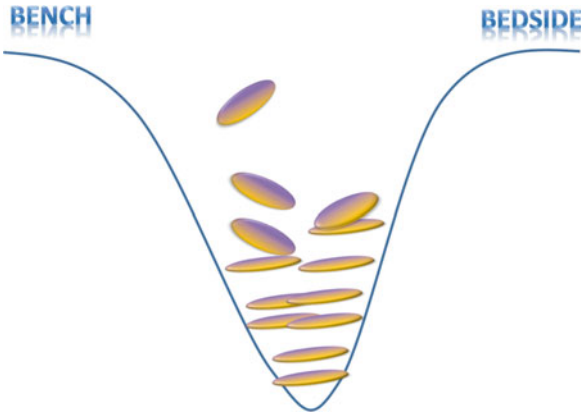


Fig. 13.1 Valley of Death. Drug and device development sometimes comes to a halt if additional funds cannot be secured for the leap from the preclinical to the clinical research phase. This may happen for a variety of reasons, most typically lack of investor confidence in the potential to recoup development costs as well as a reasonable return on investment

Longer approval times encroach on revenues. Typical patents grant 20 years of exclusivity, but 12–15 years are lost to clinical trials and other research and development. A typical NDA requires 70 studies; 91,000 pages of regulatory documents, and costs $359 million. Documentation for the regulatory process (IND, NDA) alone is about 3 % of R&D costs, but still amounts to $24 million. Delays in approval cost $684,000–$1 million/day. Total estimated cost of bringing new drug to market is $800 million–$1.4 billion. These are Tufts CSDD data from 2010. Other sources such as Public Citizen estimate the costs to be much lower, on the order of $110 million overall. Public Citizen attributes the discrepancy to the following:

- Many drugs receive federal support for development.
- Drug companies deduct 34 % for R&D.
- Tufts CSDD figures include opportunity costs.

Nevertheless, regardless of methodology, cost of research is going up because study subjects are more complex, new study medications and devices are more complex, protocols are more complex, and regulatory requirements are more burdensome. Recent studies have also confirmed that the burdens of healthcare research and development costs are tilting away from the NIH and toward industry (Fig. 13.2).

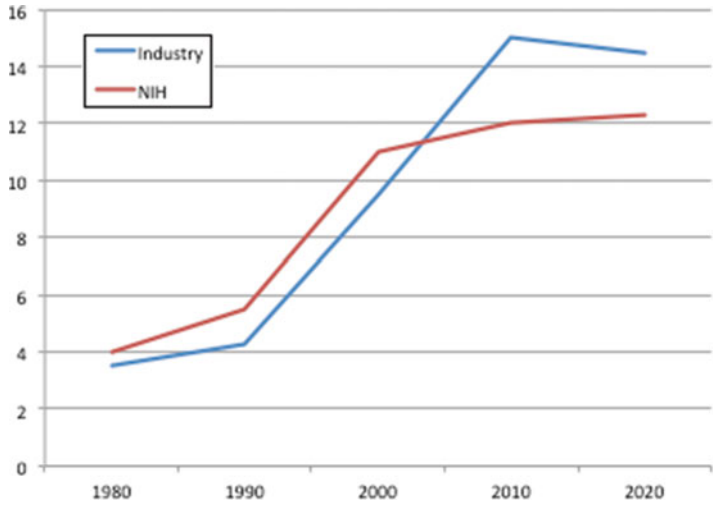
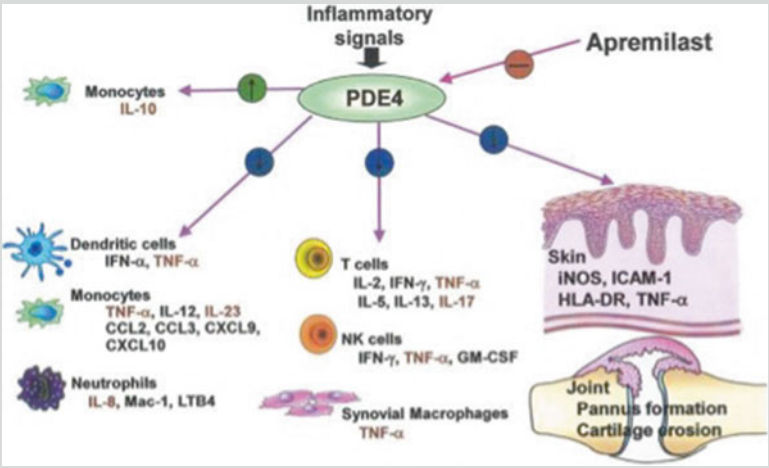


Fig. 13.2 The proportion of pharmaceutical research being funded by industry is increasing and supplanting but not completely offsetting the declines in funding from the NIH

Inset 13.1

Some studies take decades to come to fruition. The study of phosphodiesterase in inflammatory mediator began in the 1950s. Subsequently, the role of phosphodiesterase inhibitors began to be understood for inflammatory and autoimmune diseases. More specific inhibitors such as apremilast were developed in the past decade and have progressed from pilot studies to multi-center Phase III trials for psoriasis.



Kumar N, Goldminz AM, Kim N, Gottlieb AB. Phosphodiesterase 4-targetedtreatments for autoimmune diseases. BMC Med. 2013;11:96.

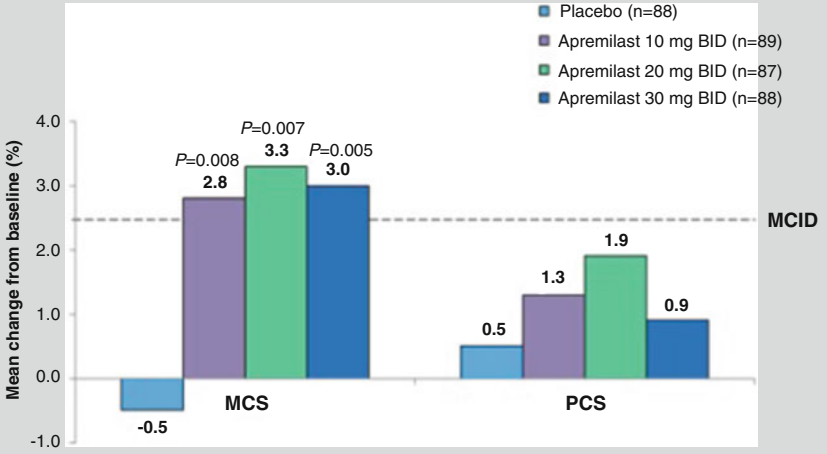
An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast. Gottlieb AB, Strober B, Krueger JG, Rohane P, Zeldis JB, Hu CC, Kipnis C. Curr Med Res Opin. 2008;24(5):1529–38.

Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, Hu C, Day RM. Lancet. 2012;380(9843):738–46.

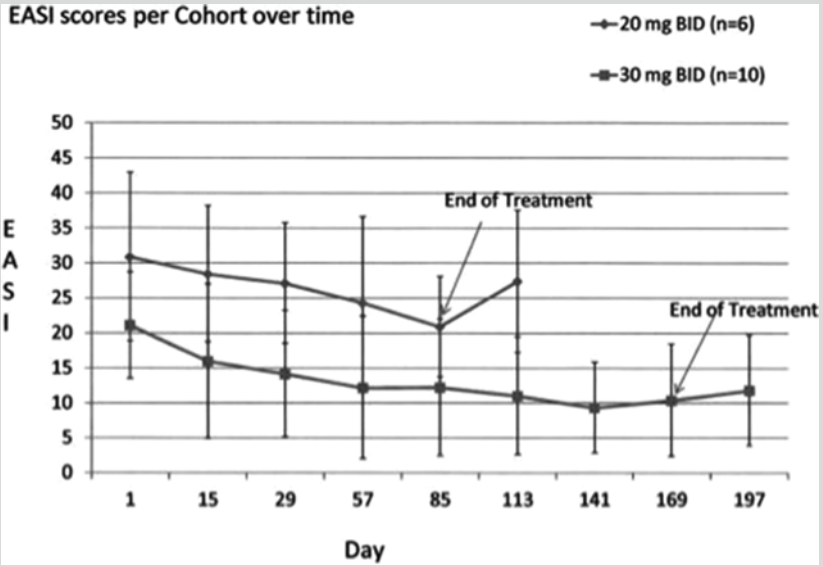
Now two Phase III Trials: ESTEEM 1, ESTEEM 2. http://clinicaltrials.gov/show/NCT01194219, http://clinicaltrials.gov/show/NCT01232283.

Strand V, Fiorentino D, Hu C, Day RM, Stevens RM, Papp KA. Improvements inpatient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. Health Qual Life Outcomes. 2013;11:82.

Apremilast has also recently been studied for atopic dermatitis. As an example of a proof-of-concept pilot study, which employs surrogate biomarkers as well as subjective improvement scores, quality of life measures, and objective clinical measures to track response, apremilast was used tested in adults. An investigator-initiated open-label pilot demonstrated small-scale proof-of-concept efficacy on a group of 16 adults with atopic dermatitis. They were treated with apremilast 20 mg or 30 mg twice daily and evaluated for (1) adverse events, and (2) for improvements in pruritus, DLQI, and EASI. Significant reductions were noted in all three measures as well as gene-based measures.



Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. Arch Dermatol. 2012; 148(8):890–7.



13.1.1 Costs of Clinical Trials

In the early mid-1970s, the cost to pharmaceutical companies of developing a drug was $100 million adjusted for inflation. Thirty years later, costs had escalated to $1.3 billion. By 2011, the costs had gone up to nearly $5.8 billion per drug.

The principal driver of cost has been the regulatory process of Phase III studies of human subjects (Fig. 13.3). Over the past decade, Phase III trials have involved more subjects and become more complex than previously. The number of procedures of clinical trials (laboratory evaluation, imaging, examinations) has increased by 70 %. There has been a commensurate increase in the burden on investigators, clinical trial staff at the investigative site and staff associated with the sponsor and trial research or management organization, leading to more staff required and more work hours required of staff members. This is even true for dermatologic studies. For example, studies of psoriasis drugs were limited to topical agents. But systemic agents such as retinoids or biologic agents such as tumor necrosis factor inhibitors

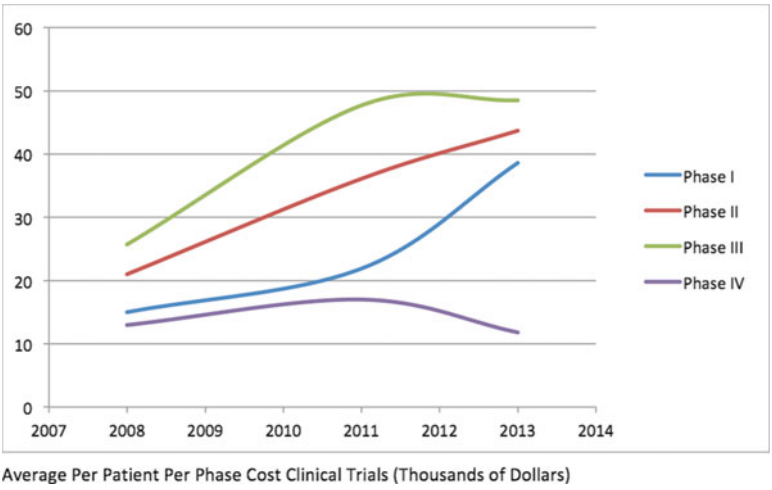


Fig. 13.3 The costliest arm of clinical drug development is Phase III

carry greater risk and require extensive laboratory evaluation. Simple examination of psoriasis subjects has been replaced by detailed PASI scores, NAPSI scores, standardized photography of psoriatic lesions, and quality of life assessments such as the DQLI. The length of clinical trials has increased by 70 %. This may be due to the complexity of the trials themselves, or to longer follow-up to observe persistence of a positive effect or the development of adverse events. Trial sizes may be larger to demonstrate a more subtle effect or to ferret out rarer side effects. Complex protocols with stringent enrollment criteria mean longer enrollment periods and higher dropout rates. This has led to a 20 % drop in enrollment rates compared to earlier trials. Because of the added burden of complex trials on subjects, the retention rate of volunteers has also dropped (by about 30 %).

Current estimates suggest that about 40 % of a company's total Research & Development expenditures go toward Phase III clinical trials. This may be an underestimate, because the overwhelming majority of new molecular entities never make it to Phase III of development. If an analysis on just those entities which are approved is done, 90 % or more of the total cost of development (from bench to bedside) is in Phase III. Furthermore, only one in 12 drugs which enter into Phase III clinical trials receive final FDA approval.

Added costs have several consequences in the industry. Small companies have difficulty sustaining the costs of trials to completion, especially if there is a glitch or setback in the study process. Investors are nervous about supporting pharmaceutical enterprises, and are quick to withdraw funds for the slightest reason (delays in clinical trial milestones, emergence of competitors, delays in FDA approval). Otherwise promising drugs and devices wither in the development phases. The result is higher healthcare costs and a dearth of potential therapies, and reduced overall quality/cost ratio of health care.

Regulatory agencies require that new drug or device application show significant evidence that a drug or device is beneficial. This should be done through well-controlled trials conducted by qualified experts. At least two studies are required, meaning two large-scale, multiyear Phase III clinical trials. These must show a benefit with 95 % statistical certainty ($p < 0.05$).

Industry is given regulatory relief in the management of rare or orphan diseases. In the case of orphan drugs, smaller and less costly Phase III clinical trials are permitted. For example, for a medication to treat paroxysmal nocturnal hemoglobinuria, approval required only 184 patients for Phase III, and 206 patients overall Phase I–III. Even for rare disease drugs, 90 % or more of the development costs are in Phase III. Some oncology drugs are given expedited approval after a successful Phase II trial.

The result is that many drugs and devices with potential benefit are not reaching patients. For example, Arena pharmaceuticals developed a drug for the treatment of obesity which was effective compared to placebo and did not demonstrate any significant side effects. Regulators did not approve the application because manufacturers were unable to show that the drug did not cause heart valve disease. Denied approval, and forced to prove a negative, the company's stock price plummeted, and its research has to go back to the drawing board. Two other antiobesity drugs were rejected that year (2011), one because the company could not prove that the drug didn't increase a subject's risk of heart attack. In effect, three proven to be effective antiobesity drugs, with trials enrolling 18,000 subjects were summarily taken down by regulators. Drugs which had the potential to reduce diabetes, heart disease, osteoarthritis, as well as a host of other ailments, including dermatologic ones, were halted, representing a tremendous setback for the management of obesity, an epidemic. Congress acted to require the FDA to take steps to support new treatments for obesity. The agency, after convening an independent panel of experts, is now reconsidering the drugs, but may require further studies costing hundreds of millions of dollars. Narrow disease-by-disease legislative action is rare and cumbersome.

Risk aversion is not just limited to regulators. Investors may pull the plug on a molecular entity in the early phases of development even if it shows promise. The reasons may vary: concern about competitors, concern about the numbers needed to show an effect, and concern about regulatory delays or denials based on the current state of the agency. This means that some products never reach the bedside.

Industry would like to see changes in the regulatory model, which it sees as outdated. Studies in the past were for acute illnesses, such as infectious diseases, where treatment results were dramatic and could be measured rather quickly. More and more current research is targeting chronic illnesses such as diabetes, hypertension, dementia, stroke, and cancer. In dermatology, treatments are aimed at managing chronic diseases such as adult acne, atopic dermatitis, psoriasis, and skin cancer. It may take years to measure beneficial effects for these conditions.

The approval process is also binary. A drug or device is approved for all its indications, all patients, and can be marketed through all prescribed channels. But if it is not effective for even one subset of the application, it is withheld from patients.

Costs of trials are high, and this cost is inherent in the current regulatory environment. Regulatory agencies have a high standard of proof, and broad authority to decide what makes a trial acceptable or not. Regulatory agencies can always ask more questions, and suggest further studies, in effect moving the bar at any point in the study process, even after Phase III trials are over. This leaves developers with a lingering sense of uncertainty over the future prospects of their discovery.

One remedy that industry seeks is an end to black/white, yes/no binary approval and a more graduated conditional or incremental approval. In this scenario, regulators could grant limited approval to drugs and devices after successful Phase II trials. The selection of patients eligible for medication would be narrow depending on the data. The income generated from early sales could be used to fund Phase III trials for final broader approval.

This model exists for FDA's accelerated approval process, which permits drugs to be approved if Phase II studies show a reasonable likelihood of clinical benefit. Currently, this is limited to severe or life-threatening illnesses, such as HIV and advanced stage refractory malignant tumors.

Agencies could modify this conditional approval by requiring companies to label products as conditionally labeled. Agencies could strictly limit broader marketing, advertising, and sales force requirements only to those devices and compounds. Manufacturers could then be granted full advertising, marketing, and sales approval after a successful Phase III trial.

The pharmaceutical industry touts its benefits to society. In the past 15 years, new heart medications (among other changes including smoking cessation), led to a nearly 50 % decrease in cardiac deaths. Since the advent of medications for HIV, the annual death rate has dropped by nearly 2/3. The pharmaceutical industry directly employs nearly half a million Americans, and indirectly supports millions of jobs in the healthcare sector.

Pharmaceutical companies are taking strategies to contain costs and maximize return on investment. These strategies include:

- Avoiding antibiotics (which are taken only once and are unable to provide a steady stream of revenue). For example, the antibiotic clarithromycin (Zithromax) is taken for a single 5-day course. In 2003, it generated $2 billion in revenue.
- Avoiding diseases affecting small populations defined in the United States as affecting less than 200,000 individuals and in Europe as affecting less than five people per 10,000.
- Focusing on chronic illnesses such as diabetes, hypertension and hyperlipidemia. For example, atorvastatin (Lipitor) is taken on a chronic basis. In 2003, it generated $9.23 billion in sales.
- Focusing on Net Present Value (NPV): a measure of return on future investment. In 2003, NPV was $1 billion for antibiotics, $3 billion for chemotherapy drugs, and $11 billion for musculoskeletal pain therapies.

13.2 Bottlenecks

In 1999, 1,800 compounds were studied worldwide in industry-sponsored clinical trials [5–7]. Ten years later that number rose to 2,950. The FDA approves 30–40 new compounds each year.

The chemical revolution in pharmacology is only about 50 years old. Prior to that, most pharmacology was plant-extract-based. Salicylic acid came from the willow tree. Opiates came from the poppy. In the 1930s and 1940s antibiotics such as natural penicillin and synthetic tetracycline, sulfanilamide, and streptomycin proliferated. Subsequent developments in rational drug design led to the development of therapies for viral disease such as that caused by herpes simplex virus. Up to the beginning of this century, recombinant DNA technology led to a profusion of vaccines, biologic medicines, and diagnostic tests.

The traditional approach to drug discovery is a battle against numbers. Out of every 5,000–10,000 unique compounds, only one leads to an FDA-approved drug. The average cost for developing each new approved drug is around $1 billion. Technology is being used to streamline development and reduce costs.

Clinical research is at a bottleneck that must be overcome for studies to be beneficial to patients. The Clinical Research Summit had a symposium: Breaking the Scientific Bottleneck. The following key points were raised at the summit:

- Clinical research is not well understood or valued by the public. While the development pipeline is growing, the pool of potential investigators is shrinking.
- Many drugs are for similar 'me too' indications.
- There is increased competition for investigators and subjects. This has led to offshoring of studies. The cost of clinical trials is much lower outside United States (60 % Canada, 40 % Poland, 30 % South Africa, 10 % India).
- Insufficient investigators are in the United States. Too few being are being trained. Many are too indebted to choose being a PI. Roughly 56,000 PI were required by 2005, 15 % shortfall by 2005.
- Foreign researchers registering with the FDA are growing rapidly
  - 1991: 5 in South America, 1 in Eastern Europe, 2 in South Africa.
  - 1999: 453, 429, 266.
  - This trend is growing.
  - In 2007, there were 26,000 global PIs, US share went from 96 % in 1990 to 54 % in 2007.
- Many trials lack adequate enrollment (1–2 % of US patients participate, only 4 % cancer patients).

Other problems include:

- High investigator turnover. Some companies view PIs as commodities, not long-term partners.
- Only 16 % of investigators have experience with more than five clinical trials.

- It is difficult to recruit volunteers. Common reasons include: a lack of awareness of clinical trials and their benefits; mistrust of investigators and the research process [8]; and increasingly burdensome and restrictive enrollment criteria (exclusion criteria have been stable, but inclusion criteria have increased almost three times between 1999 and 2005).
- Retention of volunteers may have dropped because of more demanding protocols, as well as increasing adverse events.
- Protocol design has become more complex.

Technology is driving transparency and efficiency in clinical trials. Data Transparency is on the rise, especially since the FDA Amendments Act of 2007, Public Law 110-85. Incomplete or inaccurate data can be costly. Some trials may have too many unexpected and uncontrolled variables, making data entry and analysis complex and difficult to follow. Upon review, the FDA may reject the trial's data. This happened to ImClone's chemotherapy drug cetuximab (Erbitux). The FDA refused to consider the drug's data, and the company founder sold shares before telling investors the news. In 2001, Bristol Myers Squibb purchased $2 billion of ImClone stock before the news was disclosed. Subsequently cetuximab was approved for its original indication and is now being explored for some refractory and metastatic skin cancers. Data transparency can be attributed to electronic data capture (EDC). EDC has its pros and cons [9–12]. Industry likes electronic data capture.

- Cost per page reduced by 80 %.
- Errors reduced by 90 %.
- Time to database lock is shortened.
- Cost savings can easily approach $350K for a Phase II trial, and $6 million for a Phase III trial.
- Real time shipping data are available, making logistical support of individual sites easy to manage and always up to date.
- Data fits FDA ALCOA requirements (data are automatically attributable, legible, contemporaneous, original, and accurate).
- Subject diary compliance is 94 %.

The downside is the mostly felt by investigators and the study site. A 10-min exam may require an hour of data entry. Software vendors don't have standardized formats and require individualized training, unique passwords, and different operating systems and support staff. If you have multiple passwords, different support hotlines in different time zones, a plethora of in-person and online software training programs, and use a particular EDC program only once, you may forego potentially lifesaving trials for those with easier-to-use EDC software. Do not underestimate the costs and inconvenience of electronic data capture. Be sure you budget the extra time you and your staff need if you are dealing with an EDC system. There are moves afoot to make EDC easier. Standardization is one of them. Examples of standardization tools include eDISH (electronic tool for drug-induced serious hepatotoxicity), and FIREBIRD (Federal Investigator Registry of Biomedical Informatics Research Data).

13.3 Administrative Delays

Bottlenecks can include IRBs, but more often it's contracting and negotiating. These typically involve many parties: the PI, CRO, IRB, insurance company, shipping and laboratory vendors, legal departments and billing departments. As an example, process mapping at Vanderbilt University Ingram Cancer Center shows the approval process requires 20 steps, and 13 decision points. The mean time to open an oncology trial is 178 days, 100 days consumed by contract negotiations. Overseas, this takes even longer: 182 Western Europe, 207 Eastern Europe, 262 in Asia, 37 in United States/Canada w/Central IRB.

The Global Recession in 2008 also put pressure on the migration of clinical trials overseas. Oncology, pain management, and rheumatology have seen the greatest growth.

Medical devices can take up to 15 years and up to $350 million to reach approval. The phases of device development include basic research, where the nexus of biology and physics are studied. The applied science phase involves developing a prototype. The engineering phase converts the prototype into a mature calibrated device suitable for clinical use. Clinical trials are part of the final commercialization stage. The classes of devices are stratified by risk: I (i.e., surgical gloves), II (syringe), III (pacemaker).

Fast track approval is granted for medications which treat serious or life-threatening conditions [12]. In 214, the FDA granted fast track approval for combination therapy with BRAF (trametinib) and V600E or V600K (dabrafenib) inhibitors for advanced metastatic melanoma. This was done based on the results of a Phase I/II trial of patients with Stage IIIC or IV melanoma and the requisite susceptible mutations.

13.4 Line Extensions

The long time to develop and gain approval of products has also eroded the period of marketing exclusivity. In the 1970, patent protection typically gave a drug company 10.2 years on the market over its competitors. In 2005, that number dropped to 2.5 years. Because patents are time limited and marketing approval lengthy, the FDA has granted patent extensions of up to 3 years for medications that can have a second indication. Companies can also get 6-month patent exclusivity if they determine a pediatric indication for an approved medication.

Pharmaceutical companies voluntarily conduct trials after FDA marketing approval. These can look at clinical outcomes, comparison trials against competitors, pharmacoeconomic studies, quality of life studies, and subpopulation studies (such as the elderly, children, minorities, immunocompromised adults, etc.).

The R&D budget of most pharmaceutical companies as a percentage of sales is 13–20 %, and the cost of clinical trials continues to rise. It has gone up 2.5-fold in the past decade alone. Only 2 out of 10 marked-approved drugs make a profitable

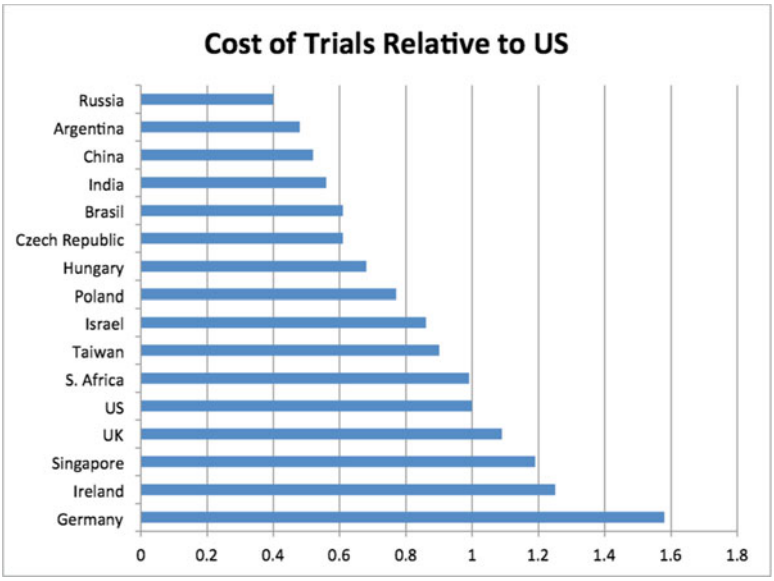


Fig. 13.4 Among many factors contributing to the migration of clinical trials outside the United States and Western Europe is cost. Significant cost savings for each phase of clinical research can be realized in Eastern Europe, Asia, Latin America, and Australia

return on their investment. There is financial pressure on drug companies to reduce costs from payors. As patent pipelines run dry—a significant number are expected to in 2015—pressure from competitors such as generics manufacturers further erodes drug company revenues. In 2009, generics accounted for 74 % of all prescriptions filled in the United States. Generic drugs cost about 1/7 as much as their brand name rivals.

To save costs, pharmaceutical companies are becoming more risk-averse, and moving abroad (Fig. 13.4). They are more likely to terminate studies at earlier and earlier phases of development for reasons unrelated to safety and/or efficacy. Trials are shifting overseas, and more than half of all FDA-governed investigators are now non-US based, and over a third of Phase III trials are conducted outside the United States, Canada, and Europe.

The pharmaceutical industry is also concerned about drug importation. They are concerned about adulteration of drugs manufactured abroad, the economic impact a bottoming out-of-import drug prices would have on the US industry, and the flouting of intellectual property laws in some foreign countries.

Speeding up trials and reducing costs are two of the objectives of the Critical Path Initiative [12]. This allows microdosing of drugs at 1 % of the recommended dose (up to a total of 100 μg) to small groups of volunteers [8–11] in order to study pharmacodynamics and pharmacokinetics and allowing sponsors to extrapolate what might happen with higher doses. This would allow manufacturers to decide

which member of a family of potentially toxic drugs (for example, chemotherapy drugs) to select for further study in larger groups of subjects at higher doses.

The FDA is also allowing manufacturers to assay surrogate markers of disease progression or remission. For example, CD4 counts or viral loads may be used for determining the efficacy of an HIV treatment, or circulating biomarkers of cancer cells may be used as early determinants of the effectiveness of a cancer therapy.

The concerns about microdosing studies are that they may bypass traditional informed consent because many preliminary animal safety studies are waived for Phase 0 trials. Critics also cite the microdosing trial of a monoclonal antibody (TGN1412 also called CD28-superMAb) that led to serious consequences in healthy subjects at 1/500th the safe animal test dose.

Adaptive clinical trials are also on the horizon as a cost saving measure to provide industry relief. In some cases, clinical trial outcomes are less than desirable because the trial is set up incorrectly for the drug or device being studied. Sometimes wrong trial set up is only discovered after unblinding. Clinical trials set up in stages are called adaptive clinical trials. Adaptive trials stage protocols with decision points and end points which can lead to a new sequence of study. When certain stages are completed or endpoints are met, the trial is assessed, and modified as needed for continuation.

13.5 Challenges to Industry

13.5.1 PhIRD-SD

There is an acronym for an industry slump known as the Pharmaceutical Industry R&D Slowdown (PhIRD-SD). Initially, it was described by Dr. Janet Woodcock, FDA Chief Medical Officer in 2004 in a paper titled "Innovation or Stagnation—Challenge and Opportunity on the Critical Path to New Medical Products." Businesses developing new drugs and devices are being challenged with higher costs, lower productivity (the low hanging fruit has already been picked), and increased regulatory burdens. This combined with lower projected reimbursements and demands for comparison data (from CER initiatives), superiority over existing compound data, and outcomes data adds to the risks for manufacturers.

Factors driving PhIRD-SD include lack of accurate understanding of disease pathophysiology, and inadequate bench-to-bedside science [13–16]. This leads to high rejection rates of compounds and to a low ratio of potential to proven successes. High profile safety concerns, increasingly complex clinical trials, a ticking patent expiration clock, and quarterly demands from shareholders add to a corporate culture of risk aversion. All of these may lead to a severe disruption of the industry. There may be a smaller R&D pipeline. There may be clinical trials done in smaller populations based on genotype. Disease research models with a high rate of return (orphan drugs, fast track oncology drugs) may be overrepresented in trials and those

with a low rate of return and higher regulatory risk (such as antiobesity drugs and antibiotics) may be ignored despite their effect on a larger population and hence, greater societal burden.

13.5.2 Addressing the Challenges

Globalization is a key initiative of industry. Markets in developing countries have the greatest potential for growth. Industry will seek to harmonize regulatory and research practices and protocols to streamline global development and marketing of drugs and devices. Harmonization means one set of rules globally, which reduces the inefficiencies of duplication and redundancy. Even something as simple as different timelines for approval of clinical trial application by country creates a regulatory burden on industry.

Industry wants to adopt a safety culture. This means a blame-free culture that permits errors to be made in order to spur innovation, but builds in systems to protect human subjects from adverse and unintended consequences. A safety culture promotes honest unfettered acknowledgement of mistakes and internal mechanisms for corrective action and improvement.

Industry wants to develop paradigms using technology to speed innovation and reduce costs. Information technology and genomics are being implemented for shortening the cycle time of identifying and testing products. Biomarkers and surrogate markers are being adopted as indicators of disease status. These may yield early results and allow go no-go decisions to be made sooner. Microdosing studies and adaptive clinical trials are other ways regulators are trying to address industry backlogs. Technology is also being used to make clinical trials more efficient, whether for data collection, data entry, or data analysis. For example, facial recognition software to count acne lesions by location, size, and type can standardize evaluation of subjects in acne trials and reduce investigator bias and intra-investigator and inter-investigator variability during visits.

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Chapter 14
Societal Perspective

Adnan Nasir

14.1 Society Needs Clinical Research

One of the ethical principles of medical care is beneficence. Our work as physicians should be of benefit to us, to our community, to society, and to the fund of knowledge which promotes human health and welfare. An obvious component of beneficence, and the subject of this textbook, is clinical investigation. Most of us have benefited from public largesse during our training, whether in medical school, or residency training, or during practice in the care of Medicare and Medicaid patients. Some have argued that physicians who are capable of conducting clinical research have an obligation to do so. Many potential US investigators have declined for a variety of reasons: lack of exposure to research during clinical training, the enormous time commitment, mounting administrative and regulatory burdens, and declining revenue. These combine to make it hard to recruit and retain physician investigators. In 2005, nearly half of PIs conducted one and only one study in their lifetime.

The group Public Agenda discusses the role of the government in allocating resources for health care. It asks questions about how research should be done and to what ends. For example, should research focus more on basic biology, or applications such as diagnosing and treating diseases? Should the diseases be common, or rare, or those with the greatest cost to individuals and society? Should disease research focus on scientific outcomes (i.e., $p<0.05$) or quality of life? How should resources be divided between research on the prevention of diseases compared to the treatment of diseases?

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Inset 14.1

There is a trend toward quality of life research.

Teledermatology: This is a study from a Patient Perspective and examines Quality of Life in a randomized controlled trial of teledermatology. The trial also shows a negative result. In this study, two sites affiliated with the US Department of Veterans Affairs were compared in a parallel group randomized trial to determine the impact of teledermatology on quality of life. Volunteers were randomized to either receive standard dermatology consults, or teledermatology consults of the store & forward variety. Of the 392 who enrolled, 326 completed the study and filled out Skindex questionnaires at 0, 3, and 9 months. Surprisingly, no differences were noted in Skindex scores, in health status outcomes, or in satisfaction with care. The results may have been skewed by the population.

Effect of store and forward teledermatology on quality of life: a randomized controlled trial.

Whited JD, Warshaw EM, Edison KE, Kapur K, Thottapurathu L, Raju S, Cook B, Engasser H, Pullen S, Parks P, Sindowski T, Motyka D, Brown R, Moritz TE, Datta SK, Chren MM, Marty L, Reda DJ. JAMA Dermatol. 2013;149(5):584–91.

Eczema Education: This study examined the role of secondary prevention on hand eczema. Volunteers with a diagnosis of hand eczema were either divided into a control group, or an intervention group. The intervention group was patch tested. They were instructed to avoid any relevant allergens. They were given specific information about hand care including the avoidance of hot water, wetting the hands prior to soaping, and drying the hands carefully. They were discouraged from wearing rings, and encouraged to use disinfectants and lipid-rich fragrance-free moisturizers. They were told to wear gloves during wet work and when handling medicines, cleaners, or foods. The intervention group had a significantly lower hand eczema severity index and a higher dermatology life quality index score.

Skin care education and individual counselling versus treatment as usual in healthcare workers with hand eczema: randomized clinical trial. Ibler KS, Jemec GB, Diepgen TL, Gluud C, Lindschou Hansen J, Winkel P, Thomsen SF, Agner T. BMJ. 2012.

What are our obligations regarding disease selection? Should we conduct research on lifestyle drugs (such as hirsutism therapy using river blindness medications) instead of better antibiotics to combat resistant infections? Should we be profiting enormously from orphan drugs which have special research patent protections but cost patients terrible sums?

14.2 The Demographics of Society Are Changing

14.2.1 Gender

Gender imbalance is an important area of clinical research that needs correction. The Belmont principle of justice includes distributive justice, which means that all individuals have a right to safe and effective therapy. If well-controlled studies have not been done in a subset of the population, it may not get the best (let alone correct) therapy for certain diseases. There are several large biases which lead to fewer studies in women. One is the male bias, which is a tendency for observers to adopt the male perspective when it comes to disease. The second is the male norm, which depicts the male situation as the "norm" and the female, or pregnant situation as "deviant." So, medicines tested in men have been extrapolated for use in women. But women have a different physiology and possibly different reaction to medication than men. From an adverse event perspective, it is known that some women are more vulnerable to dysrhythmias with antidepressants than men. Some biologic drugs (such as TNF alpha inhibitors), and some antihistamines can affect the QT interval and may have different side effects in women. Conversely, women have been the sole subjects of studies on contraception, with its attendant short-term and long-term risks.

The most recent recommendations for clinical research involving suggest disclosure for origin of tissue culture cells (whether male or female). In clinical trials involving women, the stage of the menstrual cycle should be noted in each subject at each study visit to monitor for hormonal effects on safety and efficacy. Clinical journal editors are advised to encourage data analysis by gender.

Originally, it was thought that preventing women from participating in clinical trials protected them. Since the 1960s, this thinking has been considered paternalistic and discriminatory. Women have been excluded from major trials on cardiovascular disease (MRFIT, Physicians Health Study). Part of the reason is protecting women, part of it is the complexity of evaluating hormonal cycles. Now, the role of estrogen in preventing heart disease in women is just being understood.

Bias comes from two sources. Male Bias is the observer bias from adoption of a male perspective. In heart disease, the studies were designed and funded by men. Male norm is the tendency to view the male experience as the standard or norm, and female differences as being deviant from the norm. Investigators didn't even think that CAD affected women at all, or it affected them differently.

Until recently, all medications have been tested on women. But women can respond differently. For example, antidepressants and antiarrhythmics affect women differently, who are at greater risk for QT prolongation and torsades de pointes.

Women have unfairly been the bulk subject of research on contraceptives and fertility. Women of color bear a greater risk for studies on contraceptives, especially poor Puerto Rican women rather than wealthy Caucasian women. The argument for doing this was that Puerto Rico was undergoing a population explosion and had a greater need for affordable contraception for impoverished women. The

US Indian Health Service imposed Norplant on Native American women without their consent. Other groups have proposed requiring Norplant as a condition for receiving welfare.

Quinacrine is used for sterilization when instilled in the uterus. It's a cheap alternative to tubal ligation in developing countries. It can inadvertently be used to control large populations of women. Some questions raised by quinacrine include:

- Women's attitudes about contraception and pregnancy
- Power inequality between men and women
- Lack of social support for many women
- Coercion by medical providers and government agencies

Because quinacrine was already used for malaria, it was not considered new or untested. No new safety or toxicity studies were done, although intrauterine instillation was a new route of administration. All of the women getting the treatment were poor, low income, of color, and poorly educated, violating the Belmont principle of distributive justice. The principle of autonomy was also violated in the quinacrine study. Hundreds of thousands of women received quinacrine sterilization without adequate information or presentation of alternatives.

Women have a shorter life span with AIDS than men, because they were not given any attention regarding the disease until 1994. With the profound birth defects associated with thalidomide and vaginal cancer with DES reinforced the idea that women and fetuses were vulnerable. In 1977, the FDA barred women of childbearing potential from participating in drug trials. In 1985 the US PHS Task Force on Women's Health Issues concluded that women were harmed by lack of research.

In 1993, the Office of Research on Women's Health was formed. In 2001, the IOM made the following recommendations: researchers should disclose whether tissue cultures come from males or females; the stage of the menstrual cycle should be noted in studies to correlate hormonal effects of toxicity and efficacy; journal editors should encourage data analysis by sex.

Recruitment and retention of women is difficult. Partly this is due to risk-taking behavior differences. Also women are caregivers with limited time. Culturally they may be reluctant to put their personal needs above the needs of others. Strategies to improve retention include:

- Providing childcare
- Providing transportation
- Flexible appointment times
- Women have a higher protocol completion rate than men

Women may be less likely to volunteer for clinical trials. They may be more risk-averse. They may not have time, especially if they are caring for children and other relatives. If they work, they may have fewer save any sick leave for themselves or caretaking, leaving less time available to participate in studies. Study sites wanting to recruit and retain women may wish to have flexible scheduling hours, on site child care, and suitable transportation arrangements.

14.2.2 Race

Minorities, particularly African Americans, have a sad legacy of mistreatment and mistrust at the hands of scientific investigations of deplorable ethical misconduct. They are more likely to believe that physicians will hide the risks of research from that, that investigators will deliberately expose them to unnecessary risks, and ask them to participate in research that might be dangerous or harmful. They believe that physicians will perform experiments on them or prescribe them medication or treatments without their consent. To overcome barriers to clinical research on minorities, the NIH is emphasizing cultural competency among clinicians, and encouraging the recruitment, training, and development of minority investigators.

Because of the Tuskegee Study, there is a great deal of mistrust among African Americans of medical research. More recently, HIV trials were done on foster children of color. Another study called the Nigerian Tuskegee experiment covers a meningitis trial there. Both of the latter two may have suffered for deliberate internet rumors. NIH is looking for more minority investigators. Furthermore, trial results have often not resulted in tangible benefits to the minority community. Minorities may have less time to devote to studies. Poor minorities may be more easily recruited with financial incentives.

Retaining minority participants can be challenging if they are also poor, because they may lack the authority, time, and resources to get away from what meager job opportunities they have in order to fulfill their volunteer commitments. They may also lack easy transportation and flexible work arrangements. Conversely, if they are poor, they may be more likely to seek reimbursement in exchange for participation, making them vulnerable targets for unscrupulous investigators and sponsors.

Inset 14.2

Health Literacy

The FDA mandates minority participation in trials. In 2000, President Clinton signed Executive Order 13166 "Improving access to services for persons with limited English proficiency (LEP)." This expanded the directives for involvement of subjects with limited literacy. There is a misconception that LEP is confined to minorities and immigrants. Actually, the greatest numbers are Caucasian and native born. According to the Institute of Medicine, 90 million Americans have limited health literacy. In 2002, about 21 % of adult Americans were found to be functionally illiterate, and 60 % were over age 60. An additional 25 % were marginally literate.

The Joint Commission says 44 % of patients who signed an informed consent did not know the exact nature of the operation performed, and 60–70 % did not read or understand the information on the form. This is reviewed in

detail in the IOM's Health Literacy: A prescription to End Confusion. According to Claudette Dalton of University of Virginia:

- Fifty percent of all patients make medication errors.
- The error rate is 5× higher among illiterate patients.
- Literacy is the single best predictor of health status.
- Diabetics may have problems with literacy because of retinopathy, complexity of their disease, and memory varies with blood glucose levels.
- She has developed tools to determine literacy:
  - How do you get your information?
  - What things do you like to read?
  - How satisfied are you with how you read?

There are steps you can take to gauge and compensate for a subject's reduced literacy. Rather than asking yes/no questions, or do you understand questions, have volunteers summarize their understanding of what you say. This teach-back method improves understanding, compliance, and reduces cost. Multimedia may help consent in patients with reduced health literacy. Having an interpreter is essential for non-English speakers.

14.2.3 Religion

In 1999, 18 % of community hospital beds belonged to a hospital with a religious affiliation, 70 % of them Catholic. About half of religiously sponsored hospitals are the sole providers in their regions. With consolidation in healthcare, Catholic hospitals have been merging with secular hospitals lately. They abide by ERDs (Ethical and Religious Directives) Women at these hospitals may be prohibited from participating in a trial requiring contraception. They may also not have access to embryonic stem cell- or fetal-based therapies for diseases such as macular degeneration, diabetes, Parkinson's disease, or to vaccines made from fetal tissue stem cell lines. End-of-life care is different at these hospitals. Feeding tubes may be mandated as well as other life prolonging interventions which lead to chronic infections and resistant organisms.

14.3 The Demographics of the World

Changing demographics will have implications for the allocation of resources for promoting global stability and health. By 2020, United States will be about 4 % of world population. Developing countries will make up 84 % of world population.

Currently about 90 % of total healthcare expenditures go to 10 % of the world's population, while 10 % of the resources go to the remaining 90 %. However, addressing health problems abroad can lead to greater security at home. Malnutrition and disease lead to poor productivity and contribute to domestic and global stability in developing nations. According to Peter Hotez of George Washington University, medical diplomacy may be an important and cost-effective tool for promoting global security and stability. Promoting the health and welfare of emerging economies can help citizens become self-sufficient, promote social and economic development, and prevent conflict and strife. Addressing global health through priority-based study may have a better return on investment than military spending as a means of promoting global stability and preventing hostility.

14.4 Resource Allocation

With finite resources, the way in which funds are expended on research and development raises a series of ethical dilemmas. Should we spend more money for applied research especially for common diseases, like diabetes? Should we spend more for basic research? This would leave drug companies funding clinical applications. Should we spend public money on basic healthcare for all? A careful analysis of our spending priorities shows how skewed they appear. Disease-resistant bacteria are an emerging menace, but rank 86th in funding. Funding for head and spine injuries has dropped. Teen pregnancy research and prevention ranks 163rd and is dropping. Lifestyle drugs are on the rise from direct-to-consumer advertising. Some lifestyle medications, such as drugs for erectile dysfunction cost at $25 per dose, and are covered by Medicare.

Neglected tropical diseases (NTDs) belong to the "bottom billions." They receive very little attention, because they affect the voiceless, vulnerable, impoverished, and marginalized. They are self-perpetuating because they impair development, pregnancy, and worker productivity. The World Health Organization (WHO) uses DALY (disability-adjusted life year) to measure disease impact. DALYs for the following:

- HIV 84.5
- NTDs 56.6
- Malaria 46.5
- TB 34.7
- Coronary artery disease 58.6

NTDs and coronary artery disease have nearly the same DALY, but spending is 100× for CAD. Helminths have a DALY impact of 3. Yet for 2 cents/person/year, you can treat them with albendazole. Or for 25 cents/dose of praziquantel, you can treat schistosomiasis, which causes bladder and genital lesions, which increase susceptibility to HIV. Some corporations are working to remedy these disparities. For example, Merck has generously donated supplies of Ivermectin for the treatment of onchocerciasis in developing countries.

Public Private Partnerships are being developed to combat intractable health problems. Industry, voluntarily and through Public Private Partnerships and other incentive programs, is working to address some of these problems. Pharmaceutical companies are redirecting some of their funds toward charity and toward NTDs, such as malaria and tuberculosis. Pharmaceutical companies have also contributed toward making HIV medication more widely available.

Treating the bulk of NTDs with a Rapid Impact package of only four drugs (albendazole, ivermectin, praziquantel, azithromycin) will cover seven major NTDs (helminths, schistosomiasis, filariasis, onchocerciasis, and trachoma) for only 50 cents/dose. This includes the logistics of delivery, monitoring, and evaluation. So about $200M for 500 M people. Eflornithine is made by Sanofi-Aventis. The IV form was stopped in 1999 due to lack of profit. It is used to treat sleeping sickness (displacing suramin, pentamidine, melasoprol). It resumed production in 2001 for Vaniqa for $1–2/d. The DNDi (Drugs for Neglected Diseases initiative) has led to the development of fexinidazole, and Doctors without Borders kits containing Nifurtimox–Eflornithine, both for sleeping sickness. Sanofi also sells its artemisinin/amodiaquine (ASAQ) for malaria for $1/treatment course. Other initiatives include: GSK for TB, malaria, HIV, and donations of albendazole; Merck's donations for Chagas, Pfizer Trachoma Initiative, J&J Children Without Worms mebendazole donations, Novartis Institute for Tropical Diseases and Singapore Economic Development Board for research in dengue, TB, malaria. Novartis Vaccines Institute for Global Health on diarrheal illnesses.

In 2012, 13 drug companies, the governments of the US UK UAE, the World Bank, and the Bill & Melinda Gates Foundation built a program to eliminate ten NTDs by 2020. The diseases under consideration are:

- Guinea worm
- Filariasis
- Trachoma
- Helminthiasis
- Trypanosomiasis
- Leprosy
- Schistosomiasis
- Leishmaniasis
- River blindness
- Chagas disease

14.5 Factors Contributing to Migration of Trials

14.5.1 Investigator Turnover

Fewer investigators are being trained, and over half of those that participate in a clinical trial do not participate in clinical trials again. This diminishes the pool of available investigators in the United States and decreases the mentorship pool available for future generations of investigators.

14.5.2 Recruitment

It's harder to recruit study participants. The volunteer rate, even in cancer trials, is less than 5 %. Most potential subjects do not realize that there are a number of strong, overlapping, and redundant protections for human subjects research. Over the past decade, consumers have become less trusting of pharmaceutical science and of investigators, with mistrust levels going from 28 to 75 % between 1996 and 2002. There has been a tremendous increase in complaints against investigator sites submitted to the Office of Inspector General (OIG).

It's harder to keep participants in studies. They have become more complex. The number of procedures involved to complete studies has gone up from an average of 90 to over 150.

14.5.3 Protocol Bloat

Sponsors are trying to trim protocol bloat. Often, sponsors and designers of clinical trials try to gather far more data than are needed for the trial, and often end up editing, cleaning, or trimming much of it out for the final application for approval. They are now working more closely with biostatisticians and regulatory agencies to determine ahead of time the minimum required for approval and thus eliminating excess data gathering along with its attendant cost surplus.

14.5.4 Technology

The industry is moving increasingly toward electronic data capture. It can be very cost-effective for the sponsor. It reduces cost/page of data by 80 %, and the error rate/page by 90 %. Data are available in real time, and trials which are adapted can be modified more quickly and confidently. It also saves the sponsor money because problems such as inadequate enrollment, early termination, protocol deviations/violations, and safety concerns such as AEs and SAEs, become evident immediately.

Electronic data capture and electronic source documents satisfy FDA ALCOA (attributable, legible, contemporaneous, original, and accurate) requirements for documentation. Study participants who fill e-diaries are 94 % likely to comply vs. 11 % with conventional paper diaries.

Technology also allows for low cost, real time, worldwide communication and dissemination of training, protocol updates, and monitoring.

14.5.5 Reduced Regulatory Burden

Over the past decade, more than half of clinical trials are based outside the United States. Over the same period, the number of investigators based outside the United States increased threefold, while those based in the United States have continued to decline (Fig. 14.1). Trials are moving overseas because the FDA does not forbid it. The FDA used to require foreign research to be done under an IND application or by Declaration of Helsinki standards. But the latter was abandoned by the United States in 2008.

14.5.6 More Potential Subjects

More patients are needed to do clinical trials. In the United States, overall participation rate is 1–2 %, and estimates from 2005 were that 20 million subjects were needed to participate in all ongoing clinical studies. Overseas clinical trial supercenters can see many patients (some see 9,000 outpatients/day), and some specialize in certain diseases, such as psoriasis or atopic dermatitis. These types of centers do not exist in the United States.

14.5.7 Disease Variability

Diseases may also manifest differently overseas, and responses to therapy may vary by ethnic group. For example, Iressa is effective in Japanese patients, but not in US patients. There are also different dermatologic concerns in global markets.

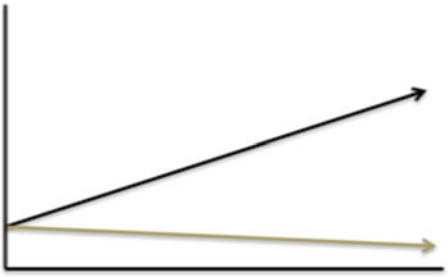

Fig. 14.1 Over the past decade, the number of clinical investigators based in the United States has remained relatively flat (gray arrow), while the number engaged in research outside the United States has nearly tripled (black arrow). There has been a gradual trend of shifting investigators and investigative sites overseas. The number of clinical trials investigators abroad has been growing at a rate of 5–15 %, depending upon the country. In the United States, there has been a slow decline in the number of active clinical investigators at a rate of 1–3 % per year. Some of the attrition is from retirement of existing investigators, and the remainder is from insufficient recruitment and early abandonment of clinical research

For example, pigmentary disorders and post-inflammatory pigmentation feature prominently as a concern among patients in Latin America, the Middle East, the Indian Subcontinent, Africa, and Asia but are less critical in Western Europe, Canada, and the United States.

Countries have different levels of attractiveness based on patient pool, cost efficiency, regulatory climate, expertise, and infrastructure. This was studied by A.T. Kearney (Bailey et al. Make Your Move: Taking Clinical Trials to the Best Location, Pharmafocusasia.com). They ranked China a close second, however, recently, it has fallen into disrepute for data fabrication and bribery.

14.5.8 Push and Pull

In summary, overseas growth is occurring because of a push and a pull. Regulations and other hindrances are pushing sponsors to do studies outside United States. Lower costs and eager investigators and plentiful study subjects are pulling sponsors abroad. A breakdown of the drivers of overseas growth follows:

- Access to patients.
- In Asia, Wyeth has identified Phase II Super Centers (9,000 outpatient visits/day; Patrick McGee "Clinical Trials on the Move").
- There are overseas hospitals specializing in diseases (heart disease, diabetes, etc.).
- Many overseas patients are treatment naïve.
- Efforts are needed to test medications in different ethnic groups (Iressa is effective in Asians, but not in the United States).
- Approved doses vary by country (Japanese doses tend to be lower in 1/3 of cases).
- ADRs differ among ethnic groups.
- Slow recruitment causes 85–90 % of the delay and is costly.
- Recruitment rates are higher, and costs are cheaper abroad.
- Local clinical trials also groom markets and grease wheels in developing countries seeking status and recognition.

14.5.9 Pitfalls

Some US plans prohibit participation in clinical trials. HIPAA makes recruitment difficult. The basic standard of care in the United States is high which competes with clinical trials. In the third world, participation in a clinical trial may lead to better care. However, as the uninsured population increases, this trend may not continue. Migration of clinical trials is not a panacea for industry. Drawbacks to overseas growth include:

- Little information on foreign IRBs.
- Difficulty in auditing foreign PIs.
- Patient understanding and education may vary.

- This calls into question adequacy of informed consent and level of volunteerism in participating.
- Lack of a skilled workforce. There is a shortage of mentors, of qualified academic staff, inadequate academic infrastructure, and a flight of well-educated well-qualified workers to developed countries. The number of physicians in Rwanda per 1,000 is 0.02, while that number is 3.58 in Sweden.
- Trend away from medical school. Applications to medical school in developing countries are down over the past 20 years.
- Lack of infrastructure. Whether referring to teaching and research opportunities or civil unrest or unpredictable electricity or inadequate roads, many factors conspire against a stable clinical research workforce.
- Diversion. Studies sponsored by multinational corporations drain already thin resources and recruit what few clinicians and scientists are in country away from pressing social needs to high status jobs in gleaming privately funded laboratories.
- Respect. Investigators in developing nations complain that their work is not recognized by grant agencies or scientific journals and is often rejected or neglected. This erodes morale.
- Cost. Maintaining and supplying a modern laboratory in a country with limited transport, limited clean water, inadequate sewage, and inadequate power requires costly importation and repair. Often, if equipment breaks down, it is not repaired because shipping parts from overseas becomes too cumbersome.
- Strife. Whether political unrest, war, or natural calamity, resources from health care are often stretched thin, treating war casualties, victims of epidemics or famine, or victims of natural disasters.
- Attitudes. Cultural and social beliefs combined with varying levels of basic education may alter participation rates or approval mechanisms for clinical trials. There may also be suspicions of caregivers of a different ethnic background than the population being studied.
- Ethics. Poor populations in developing countries are particularly vulnerable to coercion or inducement. The ethical requirements of IRBs vary among nations.

14.5.10 Cost Savings

Many US companies are shifting trials overseas because they are cheaper, and pools of subjects are larger. Issues raised include uniformity of standards and regulatory issues. Race, justice, and economics also come into play. Vulnerable populations overseas share the following characteristics:

- Limited economic development.
- Inadequate protection of human rights.
- Inadequate community and cultural experience with, or understanding of, scientific research.
- Limited availability of healthcare and treatment options.
- Limited ability of individuals to provide informed consent due to literacy, language, educational, or cultural barriers.

14.5.11 Abuses

Harvard received millions of dollars of grants for studying the DNA of Anhui people, who were promised health care which never materialized. Volunteer rates there exceeded 95 %, perhaps due to local party official coercion. The US Embassy in Beijing warned US medical researchers from working in poor areas of China where people are poor, health care is poor, and people are unable to protect their rights.

Nigerian children were studied by Pfizer for a quinolone (Trovan) for meningitis. In the study, an oral drug was given, no monitoring of progress with spinal taps was done, and no rescue medication was given if patients were worsening, and the dose was 1/3 of the dose given in US trials. In 2009, a federal appeals court ruled that Nigerian families could sue Pfizer in US courts, this is pending before the US Supreme Court. In Nigeria, officials sought $9B in criminal charges against Pfizer, and settled in July 2009 for $75M.

> Statistics are people with the tears wiped away.
>
> Dr. Irving Selikoff

14.5.12 Cultural Sensitivity

It helps to understand the local culture. One Hungarian researcher said Patients in the United States have an overdeveloped sense of their rights and fear of being harmed. In some parts of Kenya and Nigeria, researchers are not welcome to ask about subject's personal habits. Revealing homosexuality can be dangerous, making one vulnerable to attacks or death. Sensitivity to the norms of a society can go a long way toward successfully engaging study participants.

Investigators and sponsors can take steps to optimize studies abroad. Strengthening local IRBs ensures institutional transparency and rigor in the trial design and approval process. This can be augmented by training investigators in developed nations before they return home. It can be done in person and reinforced online. Provide additional health care. Communities that benefit from overall healthcare delivery as a bonus for participating in clinical trials may be more committed to participation. Technology, whether online resources, or solar power, can help maintain and sustain a clinical research enterprise. Take the long view. Study projects that have a long-term plan tend to reinforce community ties. Studies that are short-term interventional studies are best incorporated into an existing healthcare setting so that continuity of care can be maintained at the end of the study.

Subjects overseas may be less litigious and more risk tolerant than those in the United States. They may also have less access to health care, and trials may be a ready means of getting basic high quality medical service by qualified and trained personnel. There may also be fewer competing studies in some sites overseas to dilute the pool of potential volunteers.

Inset 14.3
Cultural Factors: Vincanne Adams looked at misoprostol vs. traditional Tibetan treatment for post-partum hemorrhage. Placebo was viewed as unethical by Tibetans and its use had to be modified in the protocol. Phlebotomy "takes away the life force" of Maoris. Some tissues and bodily fluids may require special ritual handling. Maori also require collective accountability and may need approval from an extended family or tribe prior to participation in a study. Transgenic animal studies are taboo ("tapu") in Maori culture. There are strict taboos against cannibalism, and incest. Maori committees reason that if human genes are introduced into animals or plants and are inadvertently (or deliberately) eaten, one and possibly both tapus will have been broken. Thus, preclinical aspects of a protocol which are based on studies in transgenic animals may be problematic to implement in Maori society. Furthermore, the Maori have a history of gods who can readily change into birds, or animals, or chimeric monsters. For humans to genetically modify cells and organisms is seen as an affront to deities, and naively arrogant.

Adams V, Miller S, Craig S, Nyima, Sonam, Droyoung, Lhakpen, Varner M. The challenge of cross-cultural clinical trials research: case report from the Tibetan Autonomous Region, People's Republic of China. Med Anthropol Q. 2005;19:267–89. doi:10.1525/maq.2005.19.3.267.

Hudson ML, Russell K. The treaty of waitangi and research ethics in Aotearoa. J Bioeth Inquiry. 2009;6(1):61–8.

14.5.13 FDA Response to Overseas Trials

Reacting to the report, FDA spokeswoman Karen Riley said the agency weighs in on clinical trials in many venues, and "is doing a number of things to enhance foreign oversight."

She added, "There is no prohibition against doing research in the developing world, and FDA expects sponsors and researchers to follow the applicable laws and regulations of the country or countries in which the trials will be conducted. Fortunately, international standards have been almost universally adopted. The next step for countries is to enforce these standards."

14.5.14 Comparative Effectiveness Research (CER)

Previous studies typically focused on comparing a drug or device to a placebo. However, in an effort to reduce costs, the ARRA (American Recovery and Reinvestment Act), wants studies to demonstrate the cost-effectiveness of new

therapies. These types of studies are very important for dermatology, where Comparative Effectiveness Research (CER) research is lacking. CER also tries to evaluate therapies in real-world situations. For example, while clinical trials for inflammatory acne may not enroll subjects with comedonal, nodulocystic, or hormone-mediated acne. Repeating trials in all subsets one at a time would be expensive and time consuming. Evaluating the effectiveness of the treatment in the real world on subjects who have different types of acne and take a variety of medications and have a variety of underlying diseases may serve patients' needs better. While an efficacy study shows that a treatment has statistically significant effects, effectiveness studies show if the treatment is useful and practical and acceptable to the population being studied.

Inset 14.4

There is a growing trend toward Comparative Effectiveness Research.

Systemic Psoriasis Therapy: A cross-sectional study of outpatients with psoriasis was evaluated for outcomes related to various therapies. A total of 713 patients were identified and were either on systemic monotherapy or narrow-band UVB phototherapy. Their psoriasis was assessed by PGA, PASI, affected BSA, and DLQI score. Patients receiving methotrexate and phototherapy showed no significant differences. Patients receiving adalimumab were more likely to be clear or almost clear (47.7 %) vs. those on etanercept (34.2 %), ustekinumab (36.1 %), methotrexate (23.8 %) and phototherapy (27.6 %). This trial showed two things. One was a regression to the mean. The effect of biologics, methotrexate, and phototherapy were less than typically reported in well-controlled trials. Furthermore, despite the statistically significant benefits of the biologics compared to phototherapy and methotrexate, there were no differences in DLQI among the treatment groups.

Gelfand JM[1], Wan J, Callis Duffin K, Krueger GG, Kalb RE, Weisman JD, Sperber BR, Stierstorfer MB, Brod BA, Schleicher SM, Bebo BF Jr, Troxel AB, Shin DB, Steinemann JM, Goldfarb J, Yeung H, Van Voorhees AS. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Arch Dermatol. 2012;148(4):487–94.

Systemic Eczema Therapy: No differences were noted in 42 patients randomized to receive either drug for 12 weeks. The evaluators who performed SCORAD evaluations were blinded. The reduction in SCORAD was 42 % for methotrexate vs. 39 % for azathioprine ($p = 0.52$). There were slightly more CBC abnormalities in the azathioprine group.

A randomized trial of methotrexate versus azathioprine for severe atopic eczema. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. J Allergy Clin Immunol. 2011;128(2):353–9.

Comparison of treatments for cherry angiomata: This is a small pilot clinical study of adult human subjects. Fifteen adults aged 21–65 were treated on three areas with PDL, KTP, or ED. All treatments were effective, but the lasers had the least textural changes.

Comparison of treatment of cherry angiomata with pulsed-dye laser, potassium titanyl phosphate laser, and electrodesiccation: a randomized controlled trial. Collyer J, Boone SL, White LE, Rademaker A, West DP, Anderson K, Kim NA, Smith S, Yoo S, Alam M. Arch Dermatol. 2010;146(1):33–7.

The ARRA stimulus of 2009 asked a variety of stakeholders their priorities for CER. Those polled included consumers, provider groups, insurers, academic institutions, and manufacturers. An online questionnaire generated 1,758 submissions on 2,600 topics. Of the 100 research topics assigned the highest priority, four were for dermatology and included: psoriatic arthritis, psoriasis, wound care, and acne. For psoriatic arthritis, the impetus is to compare different strategies of incorporating biologics into the management of different inflammatory diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis. For psoriasis, the effectiveness and impact on quality of life is being compared for topical steroids, ultraviolet light, methotrexate, and biologic agents. For wound care, the effectiveness of topical and systemic therapies is being compared of chronic lower extremity wounds. For acne, various long-term acne therapies are being compared.

The Affordable Care Act is supporting research in patient outcomes through the Patient-Centered Outcomes Research Institute (PCORI). The NIH, through the NIAMS, established the Dermatology Clinical Effectiveness Research Network (DCERN) in 2009.

One of the early studies in psoriasis looked at physician preferences for first-line therapy in moderate-to-severe disease. Phototherapy was widely preferred, but preferences varied by gender (male physicians preferred phototherapy more than female physicians) and geography (Midwest physicians preferred adalimumab). Patients from ten different were also asked to rank the effectiveness of psoriasis therapies.

Another set of studies evaluated therapy of diabetic foot ulcers. These showed that foot ulcers treated with engineered skin were more likely to heal faster than wounds treated with growth factors or platelet-based agents. Another study is evaluating the benefits of hyperbaric oxygen in wound healing. These studies are funded by companies dedicated to wound healing, as well as by the AHRQ. Other studies under review include the long-term safety of psoriasis therapies, a comparison of treatments for squamous cell carcinoma, and a comparison of various combinations of benzoyl peroxide and clindamycin for acne.

CER may benefit from electronic health records because it can allow for in-depth analysis and comparison of detailed anonymized retrospective data on large populations. Systematic collaborations and reviews such as the network of the Cochrane Skin Group can release data on the best evidence regarding alternate therapeutic paradigms.

Industry has a mixed and wary perspective on CER. On the one hand, well-conducted CER can identify therapies which have the greatest likelihood of success and are amenable to universal adoption by specific populations. Current trials have noninferiority thresholds, which are relatively easy to meet. The most effective therapy may be the one developed by industry. On the other hand, CER may show lack of superiority, effectiveness, or widespread adoption of an industry-supported therapy. In the future, the government may not approve new drugs or devices solely on the basis of statistical superiority to placebo. The government may require a statistical comparison to an existing and less-expensive alternative. The government has assured industry that CER data will not be used to restrict physician prescribing.

14.5.15 Community Research

Clinical research is founded on seven ethical principles. Research must demonstrate value of a clinical, scientific, or societal nature. Results of research may improve health, or they may add to the wealth of knowledge on the human condition. Research results should be based on valid and reproducible science, and the benefits must outweigh risks. Subject selection should be fair, and should reflect the local community. This last ethical principle, while repeatedly emphasized over the past few decades, has frequently fallen short of expectations. African Americans represent 12 % of the US population, but only 5 % of the clinical trial population. Hispanics comprise 16 % of the US population, but only 1 % of clinical trial participants. Women make up only 33 % of cardiovascular device trials.

There are a number of reasons for these disparities but the key drivers are community attitudes, subject attitudes, investigator attitudes, medical journal editor attitudes, and sponsor attitudes regarding race, gender, and age. Some communities are geographically concentrated. For example, the Zip Code Analysis Project showed that 80 % of minorities reside in 20 % of US zip codes. Lack of diversity in research can lead to disparities in outcomes and overall inequality in healthcare outcomes. Solutions include recruitment of diverse investigators, raising awareness in the scientific and business spheres, and building trust through communication and involvement of communities.

Community-based research is one means of bridging the divide. It promotes communication and builds trust through involvement of investigators, sponsors, and community leaders. Community-based research can include population studies, studies of factors which contribute to health disparities, and social, behavioral, and epidemiologic research in communities. The research can be initiated by investigators, by the community, or by a partnership of the investigator/institution and the community. Community-based research can look at all the factors lead some populations to have a greater burden of disease than others and look into interventions which may address the disparity. Studies of this nature may be useful in addressing various community factors associated with the development or exacerbation dermatoses including poverty, inadequate vaccination, malnutrition, obesity, diabetes, drug abuse, and mental illness.

Chapter 15
Opportunites in Clinical Research: Take the Initiative

Adnan Nasir

Clinical research is expected to grow as an industry in the coming decades. Demographic trends such as the aging population, increased consumption of healthcare services, demand for lifestyle drugs, growth in biotechnology industry, particularly nanotechnology all contribute to increased demand for clinical research.

There has been a 20-year average increase in life span in the latter half of the twentieth century. Fertility rates have been dropping in industrialized countries and in the developing world. Average life spans are expected to increase another 10 years by 2050. The median age has grown from 23 in 1900 to 35 in 2000. A significant increase in persons aged 65 and older is expected to surge between 2015 and 2030 (Fig. 15.1). In 2000, the proportion of US residents in this age range was 12.4 %. It is expected to be nearly 20 % by 2030, from 35 million to 71 million. One of the fastest growing subsegments of this group is expected to be 80 and older, from 9.3 million in 2000 to nearly 20 million by 2030. Many of these individuals are expected to populate states where average annual days of sunshine and skin cancer rates are highest. For example, by 2025, Florida is expected to have 25 % of its population aged 65 and older.

The ethnic composition of the United States is expected to change substantially in the coming decades. Between 1900 and 2000, the number of states with at least 10 % of the population that was not Caucasian went from 2 to 26. Between 1980 and 2000, the Hispanic population of the United States more than doubled. By 2000, three US states have majority non-white populations. Globalization of research and innovation will be confronted with the needs of ethnically diverse communities worldwide. Between 1950 and 2000, the United States and other developing nations

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A. Nasir (ed.), *Clinical Dermatology Trials 101: A Primer for Dermatologists*,
DOI 10.1007/978-3-319-09027-6_15

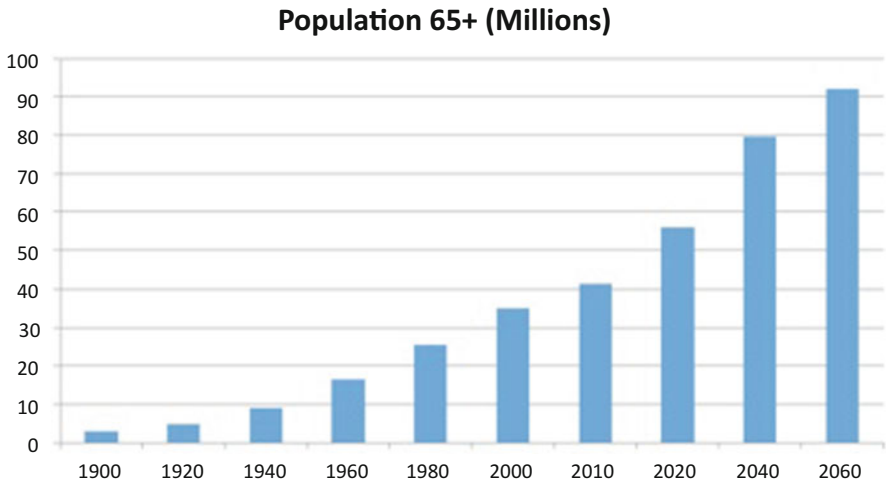

Fig. 15.1 The population of the United States over 65 has been increasing dramatically, a trend that is expected to continue (Source: US Census Data)

comprise a diminishing share of the world's population. These trends will require investigators who are sensitive to and fluent in the needs and cultures of a diverse population.

Gender composition has also changed in the United States and other developed nations (Fig. 15.2). By the middle of the last century, the United States has gone from a majority male to a majority female nation. The sex ratio of males to females has declined every decade from 1910 to 1980. This ratio increases with increasing age. Between 1900 and 2000, the number of states with a majority female population has increased fourfold, from 11 states to 44. Over the same century, the nation has gone from primarily agrarian to primarily urban and suburban in population.

From a public health perspective, older individuals will consume more healthcare services. Around 80 % of individuals aged 65 and older suffer from at least one chronic health condition, and 50 % suffer from at least two. Diabetes affects nearly 19 % of this population. Diabetes is associated with a number of cutaneous manifestations. A number of skin diseases are associated with the elderly. These can range from disorders of cell proliferation such as skin cancer, to diseases of the skin barrier, the immune response, diseases associated with metabolic and nutritional changes. The normal process of aging can also affect the skin with decreased elasticity, thinning of the dermis, fragility of the cutaneous vasculature, graying of the hair, and nail dystrophy. Infections are common in the elderly population, including onychomycosis, bacterial infections, and intertrigo. Viral infections such as herpes zoster can have severe manifestations in the elderly. Hospitalized or bedridden aged are at greater risk for pressure ulcers and institutional infestations such as pediculosis and scabies. The elderly are on multiple medications and are at greater risk for drug reactions, many of which affect the skin. Autoimmune bullous dermatoses

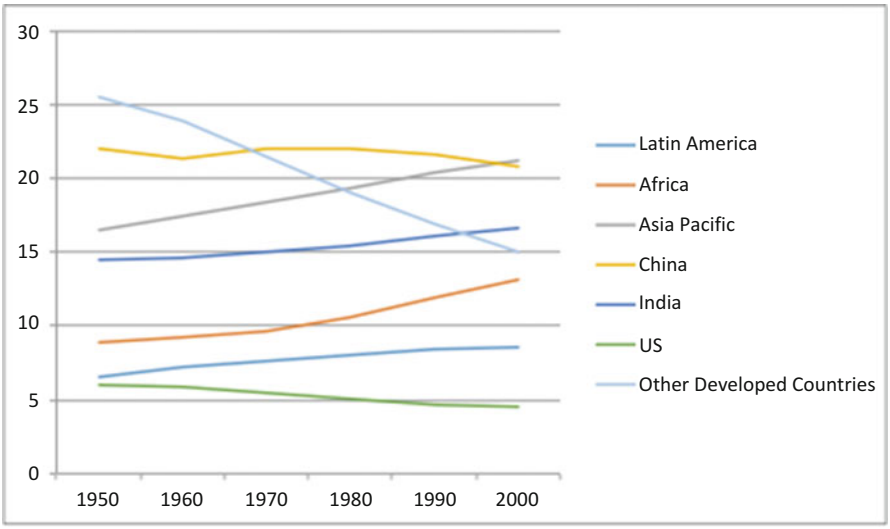

Fig. 15.2 The percentage of the world population represented by the United States and Westernized nations is declining. This is the opposite of population trends in Africa, Latin America, and Asia

such as bullous pemphigoid tend to occur in the elderly. Paraneoplastic autoimmune bullous dermatoses such as paraneoplastic pemphigus are more common in older individuals. Itch is very common in the elderly and represents a major cause of morbidity and reduced quality of life.

The demand for cosmetic dermatologic treatments for androgenetic alopecia, hirsutism associated with aging, rhytids, and therapies for improving skin texture and dyschromia will grow. Benign neoplasms such as acrochordons and seborrheic keratosis and lentigines tend to proliferate in the elderly.

Nanotechnology is the study of materials and devices 100 nm in size and smaller. It capitalizes on the unique properties of matter engineered at this size scale to create entities with novel characteristics. Nanotechnology-based materials have been developed for consumer, military, and industrial use. Dermatology is one of the fastest growing beneficiaries of nanotechnology over the past decade. Some of the top holders of patents in nanotechnology include dermatology and cosmetics companies. Nanotechnology intersects with biology, materials science, chemistry, physics, quantum mechanics, pharmacology, molecular biology, bioinformatics, genomics, and proteomics to revolutionize the diagnosis and management of skin disease and for the maintenance of skin health. Nanomaterials have been created for photoprotection, and for enhancing the appearance of the skin, hair, and nails. They are being developed for the targeted treatment of a number of skin disorders, from the use of gold nanoshells for treating acne and melanoma, to thermosensitive

nanopolymer gels for the prevention of the transmission of HIV, to liposomal nanoparticles for the delivery of retinoids and ceramides [1, 2]. While some advances in dermatology therapeutics may have reached a plateau, with "low hanging fruit" already harvested, nanotechnology is expected to broaden the horizon of discovery significantly, and greatly add to the future of skin health.

These trends in demographics and discovery have generated both an urgent demand for new skin treatments and a wide pipeline of products and technologies. As discussed in previous chapters, one of the biggest bottlenecks for bringing basic science ideas from the bench to the bedside is human subject clinical trials. The clinical trials phase is the most expensive and potentially time consuming aspect of the approval process. Delays in this phase can add substantially to cost overruns. They can also cost competitive advantage and shorten patent exclusivity. Protocols have become more complex and costly in recent years demanding even more of sophistication and training investigators and investigative site staff.

These trends make for a relatively positive career outlook in investigative dermatology. The need for clinical investigators is expected to grow by 13 % over the next decade compared to 9 % for other careers. Almost 75 % of investigators receive no formal training. As protocols and investigational products become more complex, expectations are that formal training courses and requirements will increase. The number of formal courses and training opportunities has increased. There are courses in good clinical practices as well as formal fellowships in clinical research and clinician scientist and medical scientist training programs.

Currently, there is a shortage of investigators [2–6]. It takes years to train adept clinicians to be qualified dermatology investigators. In addition to the long years of training for a medical education and residency, there is the training in the scientific method and in good clinical practices (GCPs) for the safe and objective conduct of clinical trials involving human subjects.

15.1 Clinical Trials Enhance Your Practice

By conducting clinical trials, you may become a recognized expert in your locale. Patients and colleagues can learn about studies in your practice, which may be a useful source of referrals. Speaking engagements at local, regional, and national meetings can be forums for heightening your practice's visibility. This increased visibility can lead to a virtuous cycle of increased referrals for patient care as well as potential participations in current and future studies at your site. If you become a highly sought-after investigator, you may be offered co-authorship on key publications related to your research.

Clinical trials give you a break from the routine of patient care. Conducting research trials may make you a better clinician [7]. They allow you to approach medicine and a disease from a future-oriented, scientific perspective. They require you to review and understand pathophysiology, pharmacology, epidemiology, biostatistics, and study design. They require you to understand currently available

alternatives to management of a particular disease. They expose you to the state-of-the art of a particular skin condition. Research trials often involve training which may augment or hone your clinical skills in diagnosing or evaluating a particular dermatologic disease. For many studies, you will be required to conduct complete physical examinations, review a variety of laboratory data—electrocardiograms, imaging studies—and review medical records including hospital records. This will keep your overall medical skills sharp and your awareness of a broader array of medical problems up to date. The extended contact involved with study participants with a particular disease may give you a better understanding of quality-of-life measures and other impacts of a disease on a subject and his/her contacts.

As you conduct studies, you will enhance your observation skills, and objectivity. You may take advantage of this by being a better diagnostician, or by beginning to develop and formulate hypotheses to conduct your own studies. In fact, many dermatologic therapies have resulted from such observation being put to use in clinical trials. Examples include observations of hair growth and lengthening associated with bimatoprost—originally used to treat open angle glaucoma—and minoxidil—a vasodilator developed for the treatment of hypertension; diminution of unwanted hair in subjects using eflornithine—originally developed for trypanosomiasis—and decreased flushing and telangiectasia in rosacea by brimonidine.

You will also be giving back. By offering novel therapies, and by providing care for those who can't afford it, you will be an active participant in optimizing care for your community. You will also contribute to the advancement of medical and scientific knowledge.

15.2 Clinical Trials Offer Leadership Opportunities

Due to the short supply of physician scientists (currently less than 5 % of the physician workforce), the job market in this field is excellent. They are highly sought-after to become the future leaders of medicine and dentistry. Physician scientists hold leadership positions wherever they are: in academia, government, and private industry (including pharmaceutical, biotech, and venture capital companies). There are a number of industries interested in career investigative dermatologists. These include: pharmaceutical, biopharmaceutical, biologics, contract research organization, trial management organization, site management organization, medical research facility, university, consulting company, and device manufacturer. If you work for the government, you could work at the FDA, CDER, or CBHR. Specific jobs in industry include: clinical research physician, medical communications officer, manager clinical programs, director clinical trials office, regulatory affairs director, drug safety liaison, and epidemiologist. You could work as a principal investigator, a co-investigator, study manager, medical monitor, medical director, field physician, medical writer, chief medical officer, insurance company case reviewer, laboratory director, or product vigilance director. Depending upon your knowledge of statistics or information technology, you could be data coordinator, a

biostatistician, a study designer, a clinical IT specialist, data analyst, data manager, or project manager. You could also be responsible for quality assurance as a QA/QC auditor, a technical writer, a regulatory specialist, or a QA/QC manager.

15.3 Challenges of Clinical Trials

The challenges of clinical research operations are rising costs, the majority of which go to study personnel, with salaries consuming nearly 60 % of research grants. In addition to study staff, legal fees and compliance review costs continue to rise. Malpractice premiums, training costs, and overhead are increased as trials become more complex, and study requirements more onerous for study participants and study sites [8–11].

The costs of maintaining a medical practice are also growing, for many of the same reasons. These are rising overhead, declining reimbursement, and ever greater regulatory burdens.

If budgeted and run efficiently, clinical trials can generate modest income to offset losses or at least diversify practice income. Any additional income can be reinvested in the practice, or used as a cushion to sustain the practice during ebbs in revenue.

It's harder for medical practices to recruit physicians, especially in rural areas. Pressures are discouraging doctors from continuing to practice. These include diminished income, autonomy, and increased overhead. Research can help offset some of these costs. But profit margins are suitable for most dermatology practices. Phase II trials are slightly better compensated than Phase I, III, or IV.

15.4 Training Options/Career Paths

There are a variety of formal and informal ways of developing the skills necessary to become a competent investigator. One of the easiest is through networking. You can seek out dermatologists in your area who are conducting clinical trials. Offer to help by asking to be a subinvestigator. This will allow you to review the protocol, get appropriate protocol-specific training, see study subjects, and work closely with co-investigators, the PI, medical monitors, clinical research coordinators, and sponsors. If you have the opportunity to attend an investigator meeting, take it. Investigator meetings are good ways to meet new people and to network. They also provide detailed information on the study in detailed study packets combined with online training content. You will get presentations from noted experts including: scientific background on the investigational product or device by a bench research scientist, perhaps even the discoverer of the patent. The sponsor may go over the pharmacoeconomics of a particular agent. A medical monitor will review clinical data from earlier trials. You will see raw data from PK studies are reviewed.

In-house MRAs or CRAs will cover topics related to the protocol such as inclusion and exclusion criteria, a study worksheet, case report forms, data collection, subject recruitment and retention, labs, investigational product dispensing and collecting, data entry, and adverse events. You will get presentations from laboratory personnel who discuss expected lab findings and anomalies. You will hear from regulatory personnel on dealings with regulatory agencies such as the FDA. You will also learn a lot from the discussions that ensue. For example, some attendees may question the study design, or details of the protocol. Obvious and subtle omissions or errors will be debated, sometime in great detail. You will come away from almost any investigator meeting with a deeper understanding of the clinical research process and a number of contacts to work with in the future.

There are standard web-based training courses. One of the best is the Collaborative Institutional Training Initiative (CITI) program. Recommended modules for investigators doing clinical trials include: good clinical practices for clinical trials involving drugs and devices; overview of new drug development; overview of international conference on harmonization; conducting investigator-initiated studies according to FDA regulations; investigator obligations in FDA-regulated clinical research; managing investigational agents according to good clinical practices; overview of FDA regulations for medical devices; informed consent; detecting and evaluating adverse events; reporting serious adverse events; audits and inspections of clinical trials; humanitarian use devices; and monitoring of clinical trials by industry sponsors. The National Cancer Institute (NCI) offers training on cancer clinical trials at www.cancer.gov/clinicaltrials/conducting/clinicaltrialscourse. It covers topics such as registering and credentialing for clinical trials; setting up and training your investigative team; looking for funding; finding an IRB; tips on subject enrollment and eligibility verification; record keeping and reporting; quality control; and working with referring clinicians. There are formal courses through Washington University School of Medicine in St. Louis has a Clinical Research Training Center (CRTC) which holds regular training seminars (t32.im.wustl.edu). They also have a postdoctoral mentored training program in clinical investigation (MTPCI). This program combines classroom work and structured mentorship to help its scholars become independent clinical investigators. The University of Iowa has mentored didactic courses on clinical investigation (www.icts.uiowa.edu), bench-to-bedside research, and comparative effectiveness research. The Academy of Physicians in Clinical Research (apcrnet.org) has a number of programs for professional development including seminars, webinars, and e-learning opportunities for becoming a certified clinical investigator. DIA (www.diahome.org) offers a number of meetings and courses (both live and online) to usher your staff from the beginning to the end of the certification process in becoming a study coordinator. The certificate program includes an overview of drug development, clinical statistics, project management, development of a study report, writing a clinical overview, and oversight of clinical monitoring.

A number of academic institutions have full-length in-house programs on clinical investigation. These require a significant time commitment but confer many benefits on young dermatologists interested in a career in clinical investigation.

In 2006, the Clinical Translational Science awards were granted to 12 academic centers. This grew to 62 by 2014. These are listed on the CTSA web site: www.ctsacentral.org/institutions. The CTSA consortium gives clinical researchers from different fields a common set of educational fundamentals:

- Epidemiology
- Biostatistics
- Decision analysis
- Ethics
- Legal and regulatory issues for clinical research
- Skills: developing a hypothesis, designing clinical research projects, writing grants, writing scientific papers, making oral presentations

The programs are 2–3 years long. In exchange for a 2-year commitment to clinical research, the NIH repays up to $35K/year of educational debt. Repayments also cover Federal taxes, and may reimburse state taxes. The commitment is for 20 or more hours/week. This allows young dermatologists to maintain their clinical skills while they are training for career in clinical investigation. In 2003, 1,200 students applied and 730 received awards.

The program with the most extensive offerings is based at the NIH. Through its vast experience with a variety of investigators and trainees, it has developed a template for optimal training of future investigators. The NIH has as one of its missions the training of biomedical scientists. The NIH Committee on Scientific Conduct and Ethics has written a Guide to Training and Mentoring in the Intramural Research Program at NIH which serves as a template for future investigators. It acknowledges that mentoring is essential to career development [12–16]. Mentors are expected to be interested in the future of their trainees, to have made significant research accomplishments, to network in their profession, to be accessible, and to have a good track record of building future investigators. Mentees should play an active role in their training. They should learn how to find a good research project, how to conduct a scientifically rigorous study, how to use their knowledge and research to gain independence, how to communicate their science in writing and in front of an audience, how to network, and how to be responsible and ethical in their conduct.

One aspect of mentorship and training is experience in the peer review process. Good mentors teach how to review a manuscript objectively, fairly, confidentially, constructively, and in a timely fashion. Similar peer review methods can be adapted to suit grants, or study protocols, or research programs.

The NIH has guidelines for scientific record keeping: http://sourcebook.od.nih.gov/ethic-conduct/RECORDKEEPING.pdf.

These include CITI (Collaborative Institutional Training Initiatives; https://www.citiprogram.org/rcrpage.asp?language=english&affiliation=100), Wiki for Clinical and Translational scientists Awards (http://www.ctspedia.org/do/view/ResearchEthics/WebHome), and Institute of Clinical and Translational Sciences Online case library (http://www.ictsethics.org/index.php?page=case-library).

Traditional MD/PhD programs have led to a greater emphasis on basic science research as opposed to clinical research [4]. Year-long training programs which do

not confer a separate degree have been developed to enrich exposure to clinical research. These include the Howard Hughes Medical Institute NIH Research Scholarship Program, the Doris Duke Clinical Research Fellowship Program, and the NIH Clinical Research Training Program. These programs have had varying degrees of success in promoting clinical research. One of the barriers to pursuing a career in research is debt [8, 17]. The NIH has developed loan repayment programs for clinical research, pediatric research, health disparities research, and clinical research on disadvantaged populations.

If you are looking to work in industry, you can decide between a small but fast, highly mobile and upwardly mobile company or a large established corporation. Whatever you decide, scrutinize your opportunity carefully. Make sure that you see a robust pipeline relevant to your experience in dermatology, whether cosmetic dermatology, procedural dermatology, medical dermatology, pediatric dermatology, or dermatopathology [18–20]. Make sure that the company has an experienced management team and that the corporate culture is supportive and highly collaborative. Look to see that the company pushes investigators "up" rather than "out." In other words, investigators leaving the company should have been promoted at their new position. Make sure that the company has adequate resources and capabilities to be viable and stable for your career horizon. It should have a strong financial position and should partner with other equally self-sufficient organizations.

15.5 Questions to Ask Yourself

If you are uncertain whether clinical investigation is the right path for you, use the following points to consider in making your decision [21, 22]. In order to do clinical investigative dermatology, you have to be motivated. Ask yourself if you are curious about medicine and about dermatology. Do you ask yourself questions on a regular basis regarding your patients and the treatment options they have? Is the prospect of looking for an answer, whether it may take a year or decades, whether it may involve you, or involve a village of dedicated professionals appeal to you? Does it matter to you whether or not you get personal credit for the work, or is it enough for you to be part of a team effort? You are likely to get credit if you work hard and develop a track record of success, but the credit should not be your primary motivation.

Ask yourself if you are a lifelong learner. Newer dermatologists are familiar with Maintenance of Certification (MOC) and continuing education to maintain licensure. In order to be a clinical investigator, you will constantly be training, whether it is to maintain your licensure and certification for your specialty, or to maintain your current qualifications on Good Clinical Practices (GCPs). You will learn, and sometimes relearn clinical guidelines and protocols. For example, if you study psoriasis, you may learn new aspects about the pathophysiology of the disease, the standard of care regarding comorbidities, and new treatments and devices being investigated for treatment. You may also review the Psoriasis Area and Severity Index (PASI) each time you do a study, regardless of your prior familiarity with the

rating scale. Some of your training you will be able to directly apply to your clinical practice. Other aspects of the training, such as the Nail Psoriasis Severity Index (NAPSI), may be new to you and may or may not have direct relevance to your practice. Still other aspects of the training such as quality-of-life indices (such as PSORIQoL) may refocus your attention to clinical outcomes from a patient perspective.

Depending upon the stage you are in your career, ask yourself what additional training you would like to do to become a clinical investigator. If you are a recent graduate of a dermatology residency program, you have to make the decision whether to participate in a fellowship program, or to learn clinical investigation via apprenticeship and independent study. Clinical trials have become complex and expensive. If you are early in your career, you can separate yourself from your peers by participating in a certified fellowship. You will get rigorous training, mentorship, and a significant head start in securing clinical trials. Some programs, as discussed, may help you with loan forgiveness.

When looking at a fellowship or training program, choosing one that best suits your needs is given. There are other aspects to consider. Make sure the environment is collaborative and not provincial. Look at the roster of faculty, and fellows. Look where the fellows have gone and what they have accomplished. Interview former fellows to get a sense of their experience. Make sure programs build you to eventually becoming independent. You do not want to join a program in which you are merely a tool to further the career of a faculty member. You want to get a substantial supervision early in your training, which is gradually stepped down to give you greater responsibility and less oversight as you progress. Mentors are critical to the process. Choose a mentor whose personality meshes well with yours, not necessarily a "Star Achiever." Michael Jordan was a basketball champion, but not a stellar coach. Make sure the mentor has the right perspective makes the time you need to build your career, even if it does nothing to advance the mentor's career.

When you pick an area to research with your message go big. Ask an important question. Ask it in a way that no matter what the outcome, the answer matters. Find a subject that appeals to you. If you like bullous disease, pick a project on bullous disease. If you don't like acne, don't work on it, even if your "favorite" mentor does. Also, don't be afraid to ask a question nobody has asked before. Sometimes, those are the best questions that open up new pathways to discovery. They can also lead to some of the most innovative collaborations.

Use the latest tools and techniques, but don't become attached to pet theories or methods. For example, investigators studying itch use every tool available, whether it's molecular biology, or functional MRI to understand mechanisms of itch from the epidermis all the way to the central nervous system [23, 24]. The work does not focus on a single technique, or a single hypothesis (histamine), or a single disease causing pruritus. The study of itch is an example of tackling a big question in a fundamental and collaborative way without preconceived notions and has succeeded in opening up new vistas in dermatology and general medicine.

If, for a variety of reasons (time commitment of a fellowship too long, debt, personal reasons, employment opportunity) you are unable to partake in a full fellowship, working with an established investigator and conducting independent study online or through seminars becomes a reasonable and economically viable option. This will mean carrying two loads if you are in a clinic or an academic institution. Remember that no matter how you are certified, whether via a fellowship, or on your own, recertification is mandatory.

Ask yourself if you enjoy research enough to make time for it. Running an investigative enterprise takes time and focus. You have to dedicate yourself to the process, from evaluating the feasibility of a protocol, to negotiating a contract and budget, to attending investigator meetings, to overseeing your research personnel and delegated subinvestigators, to complying with local, state, and federal regulatory requirements. If you try to do clinical research as an add-on to full-time practice, you may be overwhelmed with administrative and clinical tasks that crowd your evenings, weekends, and holidays.

Ask yourself if the culture of clinical science is appealing to you [25]. Dermatology practice, even a subspecialty of dermatology, such as immunodermatology or pediatric dermatology requires a broad knowledge base. You see the results of your effort in a relatively short period of time. Clinical investigation can take decades to come to fruition. And many clinical trials are aborted, or unsuccessful, or tabled because of financial reasons or competitors. You have to ask yourself if the process is as enjoyable to you as the outcome. In clinical investigation, progress is incremental, a process is central. On the other hand, progress can be monumental. Think how many individuals have benefited from the vaccines for varicella zoster, or human papilloma virus, or from the antitumor properties of Toll-like receptor agonists. These could never have made it to the public without the dedication of investigative dermatologists.

Ask yourself if you want to watch technology zoom past your, or if you want to be a conductor on the train. Nanotechnology will be at the fulcrum of a number of clinical advances in dermatology in the coming decades. Genomics and bioinformatics will be used to revolutionize personalized medicine in melanoma. Lasers are being investigated for topical drug delivery and the delivery of cells, including stem cells. These are heady days for the clinical investigator. The optimism and the thrills of discovery outshine some of the drearier prospects of clinical medicine, including declining reimbursements, increased governmental regulation, and increased interference in the practice of dermatology.

Perhaps you have always had an interest in clinical research and may have done a great deal of research prior to or during your medical training. Perhaps you have suppressed your investigative learnings to pursue a career in clinical dermatology but now feel the time is right to re-activate your passion for the research process.

Ask yourself if you like working by yourself or want to be engaged with a wider circle of doctors, scientists, and technical people. Ask yourself if you are in a position to complement scientists involved in drug and device discovery. With your clinical skills and ability to ask relevant questions that address everyday problems,

which are apparent to you as a dermatologist, but which might elude an experienced bench scientist. Ask yourself if you want to snap into the puzzle of clinical research as the final, vital piece.

15.6 Develop the Right Skills

Develop additional tools to help you succeed. Learn to work with and respect the contributions of scientists in academia, industry, and government. Learn to work with administrators, regulatory officials, and attorneys. Cultivate a healthy respect for your research team and become a mentor yourself. Learn to work with a variety of companies, large and small. Don't get discouraged if it takes you some time to gain traction as an investigator. The career ladder is long, and has rungs that reach very high.

Learn how to communicate well. As an investigator, you will be called upon not only to critique and understand the scientific literature, you will be asked to share your knowledge. This can be with patients, or with an audience of non-dermatologists, dermatologists, or scientists. You have to develop your skills in giving presentations. If you are not comfortable in front of a group, get help, whether from a mentor, or a speaking group in your town or institution. Make your presentations snappy, memorable, and compelling.

Learn how to write well. You can do this in several ways. Ask to review manuscripts being considered for publication. Examine the manuscripts for clarity, consistency, and logic. Look at how the authors pick their topic and develop it. See how the authors defend their claims with supporting data. Analyze the data for readability. Are graphs being used where a table would be better? Are photographs included where a diagram would make more sense? Are the materials and methods complete, or are there key steps lacking? When you review a manuscript, whether formally or informally, see if you can formulate a cogent critique. It should be organized, respectful, and pertinent. As you gain experience in reviewing manuscripts, you are ready to write your own. Ask to participate in the publication of manuscripts related to studies you are doing. If the study sponsors are not planning any publications, see if there are research topics in the study which you can publish on your own. If you have a research question, ask your sponsor if you can develop a protocol to answer it. You will learn a lot if you have to write your own protocol or a grant application for your own research project.

15.7 Go for It

It is a tremendous privilege to be a dermatologist. It is wonderful to make a difference in people's lives on a daily basis. To dermatologists, no other profession is more satisfying and rewarding. To some dermatologists, the only way to make it better is to offer our patients and society something more through a career in clinical investigative dermatology.

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Appendix

Chapter 2: Definitions

Sponsors: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial [33].

Good clinical practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected [33].

Contract research organization (CRO): An organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions [33].

Site management organization (SMO): An organization that provides clinical trial-related services to a CRO, a pharmaceutical company, a biotechnology company, a medical device company, or a clinical site. The site is usually a hospital or a similar health care institution that has adequate infrastructure and staff to meet the requirements of the clinical trial protocol.

Clinical research associate (CRA): A professional who monitors clinical trials and research studies. CRAs can be either employed by a Pharmaceutical or Biotech Company, CRO, Independent Consultant or may act as freelancers. CRAs practice FDA-approved methodology, monitor clinical trials, and ensure that clinical trials adhere to established guidelines, regulations, and standard operating procedures (SOPs) [40].

Internal review board (IRB): An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among

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other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects [33].

Independent ethics committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and nonmedical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects [33].

Covered entity: Defined in the HIPAA rules as (1) health plans, (2) health care clearinghouses, and (3) health care providers who electronically transmit any health information in connection with transactions for which HHS has adopted standards [28].

Feasibility Questionnaire

Please complete the form **and return to Susie Q at susie@pharmacompany.com**

Completion of the feasibility does not guarantee that your site will be selected to participate in any of the studies. Based on the feasibility criteria your site may be selected to participate in one study.

Completed forms are due within 5 business days

Estimated Study Timelines

Investigator Meeting	**January 2014**
First Patient Entered	**February 2014**
Last Patient Entered:	**August 2014**
Last Patient Out:	**December 2014**
Expected Enrolment Per Site	**10**

Salutation: ☐ Prof ☐ Dr ☐ Mr ☐ Mrs ☐ Ms ☐ Other _____

First Name - Principal Investigator	**Last Name - Principal Investigator**
Institution/Practice Name	**Type of Institution (e.g., hospital, university, private clinic)**
Address	**Country**
Town / City	**Zip Code/Postal Code**
Business Phone Number	**Business Fax Number**
Email Address	

Area of Specialty (check all that applies): ☐ **Dermatology** ☐ **Other (Specify):** _____

Principal Investigator Experience

1. Do you have previous experience conducting dermatology studies? ☐ Yes ☐ No
   If yes, please advise how many dermatology clinical trials you have conducted within the last 5 years: ____
2. Have you ever worked with DrugXYZ on a clinical trial? ☐ Yes ☐ No
3. Has your site worked on previous Pharmacompany clinical trials? ☐ No ☐ Yes,
   indicate Study Numbers/Indications: _____
   _____
4. Are you familiar or have you worked with the Global Skin Assessment Scale? ☐ Yes ☐
   No

Please complete the table below to reflect your current and past experience in the conduct of clinical trials (over the past 5 years):

Indication	Phase	Type of Study	Role on study (PI/sub-I)	No. of Patients Enrolled at Site	Duration of Study	Enrolment Period (months)	Did the Study Recruit to Target/Timelines (if no, please comment)
	☐ I ☐ II ☐ III ☐ IV	☐ Device ☐ Drug - indicate class: _____					
	☐ I ☐ II ☐ III ☐ IV	☐ Device ☐ Drug - indicate class: _____					
	☐ I ☐ II ☐ III ☐ IV	☐ Device ☐ Drug - indicate class: _____					
	☐ I ☐ II ☐ III ☐ IV	☐ Device ☐ Drug - indicate class: _____					

Clinical Research Staffing & Experience

1. Please indicate the number of current studies that you are participating in as the Principal Investigator? _____
2. How many of these studies are currently enrolling patients? _____

3. How many total site staff members do you anticipate participating in the study? _____
   Will Sub-Investigators be assigned? ☐Yes ☐No If **yes**, how many? _____
   How many Study Coordinators are estimated to participate in the study? _____

4. Data entry of subject information is estimated to take 1 hour/subject/week. Do you have the appropriate data entry staff to complete the data entry task?
   ☐Yes ☐No

5. Do you anticipate being involved in any other related studies which may compete with this trial? ☐ Yes ☐ No

6. Are you and your staff/clinic available to conduct study visits on the weekends?
   ☐ Yes ☐ No

7. Please indicate your clinic holidays, your clinic/staff vacation schedules, or the dates you will have limited staff to complete study documentation and/or patient study visits

   _____

   _____

   _____

Patient Population/ Recruitment-related Issues

1. How many patients with skin condition x do you see at your site per month?
   ____adult patients/month

2. How many patients with moderate skin condition x do you see per month?
   ____ adult patients/month

3. Based on the Inclusion/ Exclusion Criteria

a)	How many eligible patients would you anticipate screening per month for:	_____	Pts/month
b)	How many eligible patients would you anticipate enrolling per month for:	_____	Pts/month
c)	What screen failure rate (%) do you anticipate for:	_____	**%**

What are the challenges that you may foresee in regards to recruitment (specific to your facility/ location, unique and/or seasonal in nature)?

Describe: _____

How many months do you think it will take your site to enrol 10 patients? ___MONTHS_____

4. What techniques do you use/have used to pre-identify patients (check all that apply)?
   - ☐ Chart review
   - ☐ Staff meetings
   - ☐ Screening clinics
   - ☐ Advertising, please describe: _____
   - ☐ Site database search
   - ☐ Other: _____

5. Do you receive patient referrals from colleagues within your vicinity?
   ☐ Yes ☐ No

   If yes, please advise where these patients are referred from (check all that apply):
   - ☐ GP/Primary Care
   - ☐ Other Clinics
   - ☐ Walk-in Clinic
   - ☐ Other: _____

6. Will your patients require informed consents and questionnaires in languages other than English?
   - ☐ Yes, specify:___ _____
   - ☐ No

Study Design & Procedures

1. Do you have a dedicated room for subjects to stay while they are waiting for the next procedure or for at least 1 hour?

   ☐ No ☐ Yes

   If **yes**, please describe: _____

2. Do you have experience working with Photocentric, Inc. (photography)?
   ☐ Yes ☐ No

3. Do you have experience using a central laboratory?
   ☐ Yes ☐ No

4. Do you have a dedicated secure access/ lockable room to maintain study supplies for facial photography?
   ☐ Yes ☐ No

5. Do you have a secure (locked) storage area (room temperature, no refrigeration required) to maintain the study medication?
   ☐ Yes ☐ No If **yes**, describe area/location: _____

☐ Yes ☐ No
If **yes**, describe area/location: Study records/binders are stored in locked cabinets within a secured area of the clinic.

_____

7. Do you have a dedicated Fax machine to receive laboratory reports and IVRS faxes?
☐ Yes ☐ No

8. The expected courier for this study is FedEx. Are you able to use FedEx?
☐ Yes ☐ No
If **no**, please provide availability of other services (company name, pick-up frequency):

_____

9. Will your facility require the use of a satellite location in order to meet the enrollment goal (For example, off site laboratory services, clinics where subjects will be seen other than the primary location)? NOTE: Any satellite location utilized for conduct of the study will require qualification and inspection.
☐ Yes ☐ No
If **yes**, please describe and provide full address and distance from primary site:

_____

_____

10. Does your facility require the use of a pharmacy to dispense study medication?
☐ Yes ☐ No
If **yes**, please list contact details as well as who would be responsible for receiving study drug supply shipments: _____

11. Do you have qualified personnel available to draw and process safety blood samples when needed
☐ Yes ☐ No
If **no**, please comment: _____

_____

12. Does your site have IATA certified personnel for specimen shipment when required?
☐ Yes ☐ No
If **no**, are you willing to have them obtain IATA certification prior to study start?
☐ Yes ☐ No

13. Has your site ever worked with ABC Central Laboratory, or any other central laboratory?

☐ ABC Central

☐ Other (Specify): _____

14.

Who will be responsible for drug shipments (please list the contact details below)?

Study Medication Shipments	
Contact Name:	
Address:	
City / State:	
Country:	Zip/Postal:
Phone:	Fax:
Email:	

Equipment and Supplies

1. Do you have the following equipment/technology available at your site (check all that apply)?
   - ☐ Scale to weigh study medication (within 0.01g measure) ☐ At site ☐ Other location
   - ☐ Sphygmomanometer ☐ At site ☐ Other location
   - ☐ Body weight and height scales ☐ At site ☐ Other location

   - ☐ PC computer with Internet Explorer 6.0/7.0/8.0 or Mac computer with Safari 3.2.1
   - ☐ High speed internet connection (for electronic data capture and IVRS/IWRS requirements)
   - ☐ Centrifuge (for safety blood samples processing)
   - ☐ -20 °C or colder freezer which does not automatically defrost (for safety blood samples)

2. Does your site use a validated Electronic Medical Records system?
   ☐ Yes ☐ No ☐ Don't know if it's validated
   If **Yes/Don't know**, would you be willing to print out hard copies and sign/date for the research files? **ONLY FOR DOCUMENTATION OF MEDICAL HISTORY, NOT AS STUDY SOURCE**.
   ☐ Yes ☐ No

3. Has your site used electronic data capture (EDC) in the past? If so, please specify:
   ☐ InForm ☐ ePRO
   ☐ IVRS ☐ Other, specify:_____

4. Does your site have wireless internet capabilities with high speed connection for electronic data capture and IVRS/IWRS requirements?
   ☐ Yes ☐ No

5. Does your site have an institutional firewall that would prevent from using an external device (such as a handheld electronic diary or tablet)?
   ☐ Yes ☐ No ☐ Don't know
   If **yes/don't know**, please provide the appropriate Information Systems contact:
   _____

IRB Information

Is there a requirement to use a specific IRB?	❑ Yes	❑ No
What type of IRB will you be using?	❑ Central	❑ Local

If you selected CENTRAL IRB, which IRB has your site used (Check all that apply)?

❑ Quorum ❑ WIRB ❑ Other, please specify: _____

For LOCAL IRB: Please list contact details below

IRB Name:				
Contact person's name:				
Address 1:				
Address 2:				
City / State:				
Country:		Zip/Postal:		
Phone:		Fax:		
Website:		Email:		
How often does your IRB meet?	❑ 2x monthly	❑ Monthly	❑ Quarterly	❑ As needed
How much lead-time (in weeks) is required to submit a protocol/ ICF to be on the IRB agenda?				
Do you have IRB meeting dates?		❑ Yes		❑ No

If yes, please provide the dates of the next few meetings:

Submission Due Date	Meeting Date	Approx. Date of Approval

Additional comments on the IRB submission or requirements:

1. Do you anticipate any aspect of the study design being unacceptable to your IRB committee?

   ☐ Yes ☐ No

   If yes, please comment: _____

   _____

2. Will the patient population and/or your IRB at your site require translations of any written documents? (Examples: Informed consent form, patient authorization, patient questionnaires)

   ☐ Yes ☐ No

   If **yes**, please list languages:__

3. Does your IRB allow your site's details to be displayed on advertising material?

   ☐ Yes ☐ No

4. Have the PI, SubI, and/or site ever been audited by FDA or any regulatory agency?
   ☐ Yes ☐ No,

   If **yes**, have you received a FDA 483 or other warning letter from another regulatory agency?

   ☐ Yes ☐ No

   If **yes**, please attach a copy of the letter with this document.

5. To your knowledge, is the PI or any site staff on any of the following lists:

a. Ineligible/ Restricted to Receive Investigational Products List (US Sites Only)	☐ Yes	☐ No
b. Debarment List (US Sites Only)	☐ Yes	☐ No
c. Routine Inspection for Cause List, with an Official Action Indicated (OAI) (US sites only)	☐ Yes	☐ No
d. Office of the Inspector General (OIG) (US sites only)	☐ Yes	☐ No
e. Other regional/country-specific lists (e.g., UK British Medical Association and General Medical Council (GMC)	☐ Yes	☐ No

6. Have the PI or Sub-I ever been investigated regarding his/her medical license or DEA permit?
   ☐ Yes ☐ No

   If **yes**, please attach a copy of related documentation.

Contracts and Financial Information

Do you agree to comply with the financial disclosure requirements FDA CFR Title 21 Part 54?

Is there a contract office which oversees your research contracts?	❑ Yes	❑ No
If yes, approximately how long (in weeks) does the process take from submission to approval?		
Does your site require more than one contract? If yes, how many:_____	❑ Yes	❑ No
Are there any contract specifics that are unique to your site/ institution you can share that may help to expedite the contracts approval process?		
Who should payments / checks be **made payable** to?		
Name:		
Institution:		
Address 1:		
Address 2:		
City / State:		
Country:	Zip:	
For the Attention of:		
Tax ID Number:		
For Clinical Trial Agreement purpose ('Notice' Section), please provide the name, title, address, telephone, fax number and email of the Institution's representative that is designated to receive any notice in writing via hand-delivered, registered or certified mail, or facsimile transmission regarding the study.		
Name:	Title:	
Institution:		
Address :		
Address :		
City/ State:		
Country:	Zip:	
Phone: Telephone	Fax: Fax:	
Email: Email:		
Name and title of the **Institutional Signatory** on the Clinical Trial Agreement (This representative must have the capacity to bind the institution.)		
Name:	Title:	

Person Completing Form:_____ **Date:** _____

Title / Role: _____

Principal Investigator Signature:_____ **Date:** _____

Sample Financial Disclosure Form

The following information is requested by Pharmaceutical Company X, Inc. in accordance with 21 CFR Part 54—Financial Disclosure by Clinical Investigators, and is required to be completed by all individuals listed on the FDA Form 1572. Please complete all the information below and retain a copy for your records.

1. Protocol Number/Title: XYZ: A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of XYZ, in Adults With a Dermatologic Condition
2. Name: ☐ Principal Investigator ☐ Sub-Investigator
3. Institution Name (if applicable):
4. PI Name:
5. Address:
6. Telephone:
7. I am a full or part-time employee of Pharmaceutical Company X: ☐**Yes** ☐**No**
8. Information Collected at: ☐Initial disclosure ☐End of study ☐One year post study completion
9. Please indicate below if any of these financial interests or arrangements of concern to FDA apply to you, your spouse, any of your dependent children or, with respect to the last item, the institution that supports your activities. If you answer **YES** to any of the items listed, please provide details. ☐ Financial arrangements with Pharmaceutical Company X whereby the value of the compensation for conducting the study could be influenced by the outcome of the study, such as compensation that could be higher for a favorable result, or compensation in the form of an equity interest in Pharmaceutical Company X or in the form of compensation tied to sales of the test product, e.g., a royalty interest. ☐**Yes**☐ **No** If Yes, please describe ☐ A significant equity interest in Pharmaceutical Company X such as ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices; or any equity interest in Pharmaceutical Company X exceeding $50,000 during the time you conduct the study and for 1 year following completion of the study. ☐ **Yes**☐ **No** If Yes, please describe ☐ A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreement. ☐**Yes** ☐ **No** If Yes, please describe ☐ Significant payments of other sorts from Pharmaceutical Company X (including payments to the institution that support your activities), exclusive of the costs of conducting the study or other clinical studies, that have a total monetary value of more than $25,000 (e.g., a grant to fund ongoing research, honoraria, compensation in the form of equipment, or retainers for ongoing consultation) during the time you conduct the study and for 1 year following completion of the study. ☐ **Yes** ☐ **No** If Yes, please describe

Start-Up Checklist

☐ Original signed and dated Form FDA 1572
☐ Original signed Protocol Signature Page
☐ Principal Investigator's Curriculum Vitae (CV)—Current and signed within 2 years of study start-up
☐ Sub-Investigator's CV—Current and signed within 2 years of study start-up
☐ Medical Licensure for PI

☐ Medical Licensure for Sub-Investigators (as applicable)
☐ PI and all Sub-Investigator's Financial Disclosures
☐ IRB Approval Letter and Approved Consent Form(s)
☐ Justification Form for Use of a Central IRB (as applicable for Quorum Review IRB)
☐ Central IRB Questionnaire (as applicable for Quorum Review IRB)
☐ Fully Executed Clinical Trial Agreement (CTA)
☐ Finalized Study Budget

Other Essential Documents needed:

☐ W-9 form
☐ IRB Statement of Compliance (Local Sites)
☐ IRB Membership Roster (Local Sites)

Study BUDGET							
	Screening	Baseline	Week 12	Week 24			
Informed consent	$100						
Demographics, history	$75						
Physical exam	$100	100		$100			
Skin assessment	$75	$75	$75	$75			
Data entry fees	$50	$50	$50	$50			
Study coordinator fee	$100	$100	$100	$100			
PI simple visit fee	$150		$150				
PI complicated visit fee		$250		$250			
Patient incentive	$50	$50	$50	$50			
Urine pregnancy test	$20	20	20	$20			
Chest X-ray	$120						
Safety labs	$75			$75			
				$30			
Total	$ 915	$ 645	$ 445	$ 750	$ 2,755	10	**$ 27,550**
Screen failures up to 10	500					10	**$ 5,000**
Invoiced fees							
IRB	$2,000						
Pharmacy fees	$1,000						
Start-up fee	$4,000						
Advertisement	$5,000						
Document Storage Fees	$1,000						
Subtotal	**$13,000**						$45,550.00
Overhead	28.00 %						$12,754.00
GRAND TOTAL							$58,304.00

Chapter 4: Glossary and Acronym Guide

Clinical trial: A planned, structured investigation of a device, treatment or drug on a group of volunteers.

Clinical study: See clinical trial.

Study site: A location where a clinical trial is conducted.

Human subject: A volunteer in a clinical trial or study.

Food and Drug Administration (FDA): The US Government agency that is responsible for overseeing the manufacture, use, testing, and conduct of clinical trials involving drugs and medical devices.

Protocol: The plan for conducting a clinical trial.

Cohort: A group of people treated or analyzed in a study.

Case–control study: A type of observational study in which two different groups are observed. One group has a particular condition or is treated a particular way and the other is not. This type of study is useful to discern differences between the groups.

Cross-sectional study: A type of observational study in which researchers record information about their subjects without altering the study environment.

Double-blind study: A type of interventional trial in which neither the investigator nor the subjects are aware of the treatment assignments in the study.

Vehicle-controlled study: A type of interventional trial in which the study intervention is compared to a placebo intervention designed to be identical in appearance for the purpose of blinding the subject and investigator to the treatment assignment.

Randomization: A method of assigning subjects at random to different intervention arms of a study.

Investigational new drug (IND) program: The means by which a pharmaceutical company obtains permission from the FDA to ship a drug across state lines for the purpose of human subject research prior to the approval of a marketing application.

Sponsor: The institution or firm providing the funding for a clinical trial.

Substantial equivalence: A term indicating that a device or drug has a similar efficacy and safety profile to an already marketed device or drug. Proving substantial equivalence is a key step to obtaining marketing approval.

510(k) clearances: A section of the Food, Drug and Cosmetic Act that requires device manufacturers to notify the FDA of their intent to market a medical device at least 90 days in advance. The FDA then will determine if the device is equivalent to a device already placed into one of three classification categories.

Food, Drug and Cosmetic Act (FD&C): A set of laws passed by congress giving authority to the FDA to oversee the safety of food, drugs and cosmetics.

Good clinical practices (GCP): A standard for designing and conducting clinical trials that provides assurance regarding the ethical treatment of trial participants, the integrity of clinical trial data, and the reporting of results.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): A joint, multi-country project bringing together regulatory authorities and pharmaceutical industry for the purpose of discussing scientific and technical aspects of pharmaceutical registration.

Declaration of Helsinki: A statement of ethical principles developed by the World Medical Association to provide guidance for those conducting or participating in biomedical research regarding the ethical treatment of human subjects.

Principal investigator (PI): A physician who is responsible for all aspects of a site's performance of a clinical trial.

Subinvestigator (SubI): A person who helps design and conduct investigation at a study site.

Sponsor-investigator: An individual who both initiates and conducts a clinical trial without the involvement of a corporation or agency.

Source documentation: Location where information is first recorded including original documents, records, and data.

Source data: The information, observations, records, and results contained within the source documents that are required for evaluation of the study.

Clinical research coordinator (CRC) or study coordinator (SC): A specialized research professional working under the direction of a principal investigator.

Study monitor or clinical research associate (CRA): An individual responsible for ensuring proper data collection as well as documenting and reporting protocol deviations.

Protocol deviation: An unplanned excursion from the protocol that is not implemented or planned as a systematic change.

Medical research associate (MRA): An individual, usually employed by the sponsor, performs similar duties as the CRA.

Medical monitor (MM): An individual, usually a physician, who has responsibility to answer protocol and study related questions.

Contract research organization (CRO): An agency or firm providing trial management services.

Institutional review board (IRB): A committee established to review and approve research involving human subjects. The purpose of an IRB is to ensure that a study is safe and effective for human participation.

Site qualification survey (SQS): A process in which a sponsor or CRO determines a potential trial site's suitability for a particular study.

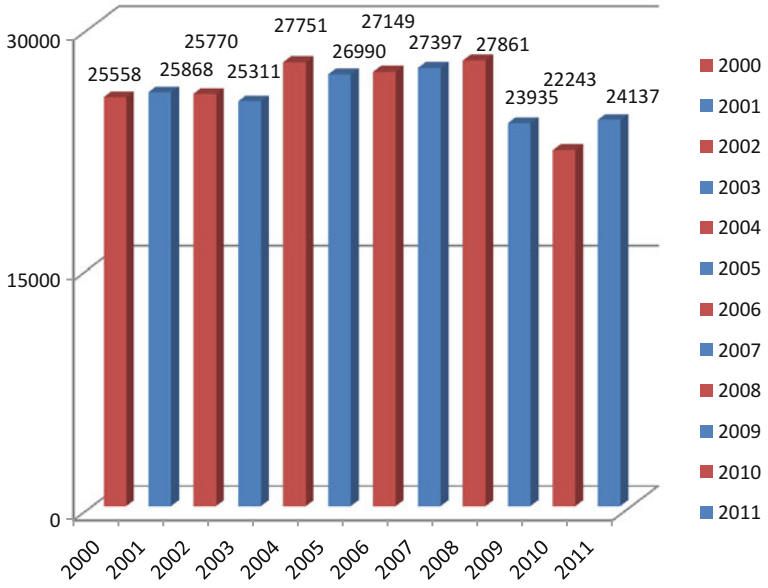
Health Insurance Portability and Accountability Act (HIPAA): A stringent set of standards enacted in 1996 to protect the privacy and security of individually identifiable health information. The act also includes standards with respect to health insurance coverage and electronic health care transactions.

Investigator initiated study or trial (IIS or IIT): A trial concept conceived by an investigator that may be conducted with or without industry sponsorship.

Medical science liaison (MSL): An industry representative or employee that is particularly well versed and able to answer scientific questions regarding a drug or device offered by a sponsor.

Physician Payments Sunshine Act (Sunshine Act): A US federal law requiring manufacturers of drugs, medical devices and biologicals to report certain payments or items of value transferred to physicians and teaching hospitals. This information is intended for distribution on a publically searchable website.

Chapter 5



Active Unique Investigators Filing Form 1572s WorldWide. *Source*: FDA's Bioresearch Monitoring Information System File (BMIS)

Adverse Event Tracking Log

Study title:										
Principal investigator:					Study coordinator:					
	Subject ID	Start date of event	Date event resolved[a]	Description of event	Severity of event	Nature of event	Relationship of event	Action with study drug 1. No action 2. Interrupted 3. Discontinued	Is this a UP involving risks to subjects or others?	Date report sent to HRPP[b]
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										

[a]All events should be resolved or noted as unresolved at the time of subjects discontinuation in the study (i.e., study complete or subject withdrawal)
[b]Report all adverse events in accordance with HRPP Guidelines

Drug Shipment Receipt Log

Date of receipt	Protocol number/name	Total number of boxes received	Ambient/ refrigerated/frozen	Name of CRC notified of shipment	Initials of CRC confirming medication received/checked in/ and placed in drug room/refrigerator/freezer

FDA AUDIT CHECKLIST

INITIAL CONTACT

☐	Staff member who received initial contact.
☐	Contact and notification date.
☐	
☐	
☐	

FDA AUDIT VISIT INFORMATION

☐	Visit start date.
☐	Estimated time of arrival.
☐	Anticipated duration.
☐	FDA Inspector contact information.
☐	Additional FDA Inspectors' names.

PURPOSE OF INSPECTION

☐	Clinical trial
☐	Investigator
☐	Routine
☐	Directed (For Cause): If directed, consider notifying legal department
☐	Follow-up (438, or warning letter)
☐	If unannounced FDA inspector arrives notify legal department

FDA REQUESTED DOCUMENTS

☐	Specific personnel requested (name, times available requested)
☐	Specific documents requested.
☐	Documents checked prior to inspection
☐	Documents requested to be sent to FDA prior to inspection.
☐	

NOTIFICATIONS OF INVOLVED PARTIES

☐	Sponsor
☐	IRB
☐	Investigator(s), Sub-investigator(s)
☐	Study Coordinator(s)
☐	Staff
☐	Laboratory
☐	Pharmacy

AUDIT PREPARATION TEAM

☐	Designated inspection coordinator.
☐	Designated FDA Inspector escort to accompany inspector at all times.
☐	Designated team member to make photocopies and take notes.
☐	
☐	

DESIGNATED INSPECTION WORKSPACE

☐	Large table or desktop cleared of all but requested ocuments.
☐	Room #
☐	Telephone number or extension
☐	Copy machine available

CLINIC, RESEARCH AND STAFF SCHEDULE

☐	Review staff, investigator, and clinic schedules
☐	Avoid conflicts of key staff from vacations, appointments, etc.
☐	Reschedule nonessential meetings.
☐	Reschedule noncritical clinic visits.
☐	Reschedule flexible clinical trial visits.

RETRIEVE RECORDS

☐	Retrieve records from storage, or print from cloud.
☐	Retrieve electronic stored records or CDs, DVDs.
☐	For hospitalized SAEs, make sure inpatient records are accessible.
☐	Have all drug accountability records available on site.
☐	Follow-up (438, or warning letter)
☐	Other

REGULATORY DOCUMENTS

	Current list of PI's active research protocols.
	Copies of all signed agreements between PI, Sponsor, CRO.
	All versions of the protocol available and dated and signed by PI.
	All protocol amendments and clarifications available.
	All versions of the Investigator's Brochure.
	All package inserts.
	All instructions for handling IP and trial-related materials.
	All IND Safety reports
	DSMB summary reports.submission documents to IRB if applicable.
	All versions of IRB approved Consent Forms.
	Original IRB Approval Letter.
	All documentation related to additional IRBs involved in study.
	IRB protocol amendment(s) and approval letter(s).
	IRB continuing review approval letters.
	IRB approval letters for revised Informed Consent Forms.
	IRB approval letters for translated Informed Consent Forms.
	IRB approval of subject compensation.
	Documentation of all payments to subjects.
	IRB approval letters for subject recruitment (handouts, ads, videos).
	IRB approval letters for Case Report Forms.
	Correspondence from the Investigator to the IRB
	Correspondence from the Sponsor to the Investigator & vice-versa.
	Original IRB letters acknowledging receipt of SAE submissions.
	Original IRB letters acknowledging receipt of protocol deviations.
	Original IRB letters acknowledging receipt of protocol violations.
	Original letters acknowledging receipt of safety reports, SAEs, AEs.
	Completed subject screening/enrollment log.
	Completed site personnel log with signed authorization of duties.
	Documentation of a trial initiation monitoring visit.
	Signed and dated monitoring visit log.
	All versions of FDA Form 1572 signed and dated.
	Financial disclosures for the PI and all sub-investigators.
	Signed and dated current CVs for the PI and all sub-investigators.
	Current licenses of the PI, Sub-I, and all other key study staff.
	GCP/HSP training documentation for everyone on FDA 1572.
	GCP/HSP documentation for anyone with more than minimal involvement in the study.
	Signed and dated current CVs for the study coordinator(s).
	Documentation of staff protocol training.
	Documentation of additional staff training.
	Documentation of protocol submission, approval, activation.

	Documentation of protocol deregistration if applicable.
	Any other correspondence related to the study.
	IRB committee membership roster.
	Documentation of any unblinding procedures and events.

	CV of pharmacist, current, signed, dated
	CV of key pharmacy personnel.
	Licenses of pharmacy personnel
	Sample labels attached to IP containers
	Signature list.
	Delegation log.
	IP accountability logs.
	Records of study product dispensed to appropriate staff member.
	Shipping receipts and records for IP and related study materials.
	Documentation of study drug transfer, return, disposal.
	Temperature logs.
	Calibration and maintenance records for all equipment.
	Certificate of analysis of IP shipped.
	Certificates of analysis of new batches of IP.

	CV of laboratory director (Central Lab, Local Lab)
	CVs of key laboratory personnel
	Licenses of laboratory personnel
	Lab certifications (CAP, CLIA, State Lab) and expirations.
	Other lab certifications.
	Laboratory normal values used throughout the study.
	Updates to normal values included in the protocol.
	Updates of laboratory procedures or tests.
	Specimen logs.
	Chain of custody SOP.
	Clinical equipment temperature logs are complete and up to date.
	Clinical equipment maintenance logs are complete and up to date.

	Complete	Incomplete	N/A or Comments
SOP			
Source Documents and medical records for each subject. Must be attributable, legible, contemporaneous, original, and accurate.			
Signed, dated, complete CRFs for each subject.			
CRF corrections properly documented (single line crosses out error, new value entered, initialed, and dated by team member).			
Inclusion and exclusion criteria for each participation have been met and are documented.			
Original signed and dated Consent Forms are on file for each subject.			
All visits are conducted within protocol windows.			
Correct laboratory blood volume in correct tube is drawn at each required visit.			
Protocol required tests and evaluations have been documented clearly, and appropriately.			
All labs are correctly labeled and match their corresponding subjects.			
All laboratory tests have been reviewed by the PI or other protocol indicated medical professional.			
Laboratory tests have been signed by the reviewing PI or medical professional.			
Laboratory values outside the normal range evaluated as “Clinically Significant” or “Not Clinically Significant.”			
Concomitant medications documented.			
AEs documented.			
SAEs reported to the IRB.			
All AEs and SAEs reported to sponsor.			
Study endpoints corrected identified and reported.			
Protocol violations and deviations reported along with corrective action plans.			
Early study termination of subjects documented.			
Study product use by all subjects documented.			
Subjects lost to follow-up documented.			
Study subject recruitment and retention plan documented.			

During audit,
Do not volunteer additional information.
Do not argue with the inspectors.
Do not sign affidavits without legal counsel.

Red flags for auditors
Lack of any errors or corrections on CRFs.
Subjects who follow protocols perfectly.
All screened subjects enroll in the study to completion.
Study staff lack knowledge about the study.
Equipment or resources at the site don't match documentation.

Common deficiencies

Failure to follow the protocol.
Protocol deviations which are not properly documented.
Failure to obtain informed consent,
Lack of accurate, complete, and current records.
Lack of accountability for investigational product.
Failure to obtain IRB approval.

Regulations do not require responding to a 483, but it is expected. A good response shows that you understand the concerns of the inspector, that you are committed to compliance and improvement, that you are serious about establishing your credibility as an investigator, and may help you avoid a warning letter.

You can respond to a 483 in person during the exit interview, or in writing. A written response tends to be more reflective, more comprehensive, and a more neutral and professional tone. Send a response within 14 days.

A good response should contain the following elements:

1. A willingness from the senior investigative team members to address the agency's concerns.
2. A point-by-point response to each deficiency noted by the inspector.
3. Corrective actions you intend to take.
4. A time course for corrective actions.
5. A plan for monitoring the effectiveness of the correction.

You may consider sending a follow-up letter to the agency which documents the results of any corrective actions you have taken. If you have any disagreement with the findings, stick to facts, and back up your facts with incontrovertible and verifiable evidence or data.

The FDA may respond after an audit with a letter. If no deviations or compliance issues are found, no letter may be sent or a general letter may be sent stating the investigator is in compliance with applicable regulations.

An Informational or Untitled Letter outlines deviations from regulations and statutes that do not meet the threshold for Warning Letters These letters typically merit a response from the investigator.

A Warning Letter identified significant violations of regulation, and requires prompt action, which must be detailed in a written response.

A Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) is sent when an investigator repeatedly or intentionally fails to comply with the protocol or its regulations or intentionally submits false information to the FDA, the IRB, or the sponsor. In these cases, the FDA will try to disqualify the investigator from participating in clinical studies and may refer the investigator to appropriate agencies for further sanctions.

Note-to-File Template

A note to file should:

- Be composed as needed based on individual cases.
- Contain clearly verifiable references to the volunteer and the protocol.
- Have a contemporary and dated signature.
- Preferably be typed or printed in neat, clear handwriting.

- Contain a succinct, precise, and accurate explanation for any errors, discrepancies, or departures from the protocol, and future corrective steps.
- Have a follow-up plan.
- Be placed in the correct section of the study binder to which it applies.

Example Note to File:

PROTOCOL #:	AMG-2015-CTAB4044-A
TITLE:	Comparison of CTAB to 4404-A on transepidermal water loss in neonates with harlequin ichthyosis
From:	Wake Research Associates
	[Kim Papadopolis, Sub Investigator]
To:	Study Volunteer File
Re:	Subject# 05-JDP
	[insert subject identification]
Date:	July 31, 2015

Dr. Jones consented the subject on July 15, 2014. Dr. Jones, in error dated the delegation of authority log July 15, 2019. The incorrect date does not reflect the date of delegation but is the result of illegible handwriting and mistranscription. Dr. Jones was reminded to print dates clearly and his staff were encouraged to question Dr. Jones if they are in doubt about the clarity of her handwriting in the future.

Signature:

Site Temperature Log

Facility Name: _____
Thermometer Name&No.: _____ Other information: _____
Sponsor: _____ Protocol: _____ Site #: _____ PI: _____
Test material name/number: _____
Required temperature range _____ Other information as per sponsor: _____

Date ddmmyyyy	Time	Actual temperature	Minimum temperature	Maximum temperature	Initials/signature for first time on current log sheet

(continued)

(continued)

Date ddmmyyyy	Time	Actual temperature	Minimum temperature	Maximum temperature	Initials/signature for first time on current log sheet

Standard Operating Procedures Manual

Table of Contents

PART A: OUTPATIENT STUDIES

SECTION 22: TRANSPORTING SOURCE DOCUMENTS
SECTION 23: DATA ENTRY

PART B: INPATIENT STUDIES

SECTION 1: CRASH CART INVENTORY AND RESTOCKING
SECTION 2: ADMISSION AND DISCHARGE PROCEDURES
SECTION 3: PK COLLECTION, PROCESSING, HANDLING AND SHIPPING
SECTION 4: SHIFT CHANGE REPORT
SECTION 5: UNBLINDING PROCESS
SECTION 6: MEDICAL EMERGENCY PROCEDURES

An Example of Regulatory Binder Table of Contents Is Below

Sec.	Essential Documents
1	**STUDY TEAM**
	Study Team Contact List
	Study Team Signature and Delegation Log
	CVs, Licenses, Financial Disclosures, Applicable Certifications of Key Study Personnel
2	**PROTOCOL**
	Study protocol + amendments
	IRB Stamped Consent Document and Translations
	IRB Stamped Advertisements
	Investigator Brochure (IB)
	Safety update letters for inclusion in IB
	Sample of Questionnaires/survey forms
	Sample of Diary cards
	Sample of memory aids for study procedures
	Any other written information given to the patient
	Sample of CRF
3	**REGULATORY**
	Committee for Protection of Human Subjects (IRB)
	IRB Submission Forms (initial, amendments, renewals, etc.)
	IRB Outcome Letters (Approvals, Acknowledgments, etc.)
	IRB Correspondence (or location)
	Food and Drug Administration
	Form FDA 1572 for all Key Study Personnel
	Copy of IND/IDE submission
	FDA Correspondence
	Annual Reports

(continued)

Sec.	Essential Documents
4	**PATIENT LOGS**
	Screening log
	Enrollment log
	Subject Visit Schedule Log
	Signed Informed Consent Forms (or location)
5	**UNANTICIPATED PROBLEMS**
	Copies of AE reports if not included in CRF
	AE log for events in non-site subjects
	AE log for events in site subjects
	Adverse Event reports
	Protocol Deviation Logs
6	**DRUG/DEVICE ACCOUNTABILITY**
	Package Insert/Prescribing Information
	Drug/Device Receipt (Shipping Records)
	Drug/Device Accountability Log
	Drug Disposal Records
	Sealed unblinding envelopes (or location)
	Individual treatment codes (or location)
	Temperature Logs
7	**LABORATORY**
	Laboratory Name and Contact Address
	Logistic Arrangements with lab (if local lab is used)
	Lab certifications and normal ranges
	Biological specimen sampling, labeling, storing and shipping procedure
	Biological specimen log
	Shipping records (if central lab is used)
	Temperature Logs
8	**MONITORING**
	Monitoring log
	Monitoring reports
	Initiation meeting information (sign in sheet, agenda, minutes, etc.)
	Correspondence
9	**FINANCIAL DOCUMENTS (may be stored in separate location)**
	Clinical Trial Agreement
	Budget
	Financial expenditure records
	Billing statements
10	**Other Documents**
	Completed CRFs (location)
	Study Closure Documentation
	Publications, presentations, manuscripts, etc.

Example of Forms, Logs, and Checklist

Study Drug Dispensing Verification Form

Protocol Number:_____ **PI:**_____

Date of Visit:_____

Subject Number:_____ **Initials:**_____

Assigned IP to Be Dispensed *:_____ **Amount:**_____

***If Assigned via IXRS, confirmation print out must be present for verification**

Dosing Instructions:

_____

_____

_____

_____

_____

Coordinator Dispensing Drug:_____**Date:**_____

Coordinator Verifying * :_____**Date:**_____

***MUST be coordinator listed on the delegation of authority log as authorized by the Principal Investigator to prepare/dispense investigational product**

Appendix A: Informed Consent Checklist (Please Refer to DHS HHS OHRP 45 CFR 46 §46.116 for Details)

Basic elements	Indicate	
	Yes	No
A statement that the study involves research	☐	☐
An explanation of the purposes of the research	☐	☐
The expected duration of the individual's participation	☐	☐
A description of the procedures to be followed	☐	☐
Identification of any procedures which are experimental	☐	☐
A description of any reasonably foreseeable risks or discomforts to the participant	☐	☐
A description of any benefits to the participant or to others which may reasonably be expected from the research	☐	☐
A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant	☐	☐
A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained	☐	☐
For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained	☐	☐
An explanation of whom to contact for answers to pertinent questions about the research and participant's rights, and whom to contact in the event of a research-related injury to the participant	☐	☐
A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the individual is otherwise entitled, and the individual may discontinue participation at any time without penalty or loss of benefits, to which he/she is otherwise entitled	☐	☐
A statement that must contain the following language: "A description of the clinical trial will be available on http://www.ClinicalTrials.gov, as required by the US Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search the Website at any time/"	☐	☐
Additional elements, as appropriate	**Indicate**	
	Yes	**No**
A statement that the intervention may involve risks to the individual (or to the embryo or fetus, if the individual is or may become pregnant), which are currently unforeseeable	☐	☐
Anticipated circumstances under which the individual's participation may be terminated by the investigator without regard to the subject's consent	☐	☐
Any additional costs to the individual that may result from participation in the research	☐	☐
The consequences of an individual's decision to withdraw from the research and procedures for orderly termination of participation by the individual	☐	☐
A statement that significant new findings developed during the course of the research, which may relate to the individual's willingness to continue participation, will be provided to the individual	☐	☐
The approximate number of study participants	☐	☐

Appendix B

PRINCIPAL INVESTIGATOR	Joe Smith, MD, PhD		
SPONSOR	Big Pharma		
SPONSOR PROTOCOL NO.	989676XMA		
PI INITIATED?	No		
CONTRACT START DATE	11/1/11	YEARS	MONTHS
CONTRACT END DATE	10/31/14	3.00	36.00
NUMBER OF SUBJECTS	10		
SUBJECT ACCRUAL RATE	2 per month		
PROJECT TITLE	A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Study Drug In Comparison To Standard of Care Drug In Patients With Serious Disease		

Comments to Postaward	INDIRECT RATE	26.0%
	Dept.CRA	$ 61,863.86
	PI	594,438.65
	Dept. Total Directs	$656,302.52
	Total Indirects	$ 170,638.65
	Total Award	$826,941.17

First Payment $23,534.62

	DIRECTS, subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
Nonrefundable Start-up Fees (not included in the PSF)	$ 16,980.25	$ 1,698.02	$ 18,678.27	$ 4,856.35	**$ 23,534.62**
Investigator's Team Budget	$ 6,300.00	$ 630.00	$ 6,930.00	$ 1,801.80	$ 8,731.79
Preaward proposal preparation fee	$ 2,200.00	$ 220.00	$ 2,420.00	$ 629.20	$ 3,049.20
IRB review fee	$ 2,200.00	$ 220.00	$ 2,420.00	$ 629.20	$ 3,049.20
CTSI review fee	$ 1,500.00	$ 150.00	$ 1,650.00	$ 429.00	$ 2,079.00
Pharmacy start-up and close out fees	$ 3,698.00	$ 369.80	$ 4,067.80	$ 1,057.63	$ 5,125.43
MRI dummy run fee	$ 1,082.25	$ 108.23	$ 1,190.48	$ 309.52	$ 1,500.00
		$ -	$ -	$ -	$ -
		$ -	$ -	$ -	$ -
		$ -	$ -	$ -	$ -

	DIRECTS, subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
Refundable Start-up Prepayments	$ -	$ -	$ -	$ -	$ -
Patient Payment Cards	$ -	$ -	$ -	$ -	$ -
Enrollment of X number of subjects		$ -	$ -	$ -	$ -

Total Payments from Visits	# of subjects	SPONSOR PAYMENT per subject	# of visits	PAYMENT per visit	subtotal per subject	Dept.CRA 10%	Indirects	PAYMENT per subject
Multiple arms, but they are the same rate	10	$ 52,980.71	16	NA, visits vary in $	$ 38,225.62	$ 3,822.56	$ 10,932.53	$ 52,980.71
						$ -	$ -	$ -
						$ -	$ -	$ -
						$ -	$ -	$ -
						$ -	$ -	$ -
						$ -	$ -	$ -

Groups providing services to subject visits	Labor directs per visit	# of visits	DIRECTS,subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
			301,971.88	$ 30,197.19	$ 332,169.07	$ 86,363.96	**$ 418,533.02**
Joe Smith, MD, PhD			$ 301,971.88	$ 30,197.19	$ 332,169.07	$ 86,363.96	$ 418,533.02
				$ -	$ -	$ -	$ -

Services included in the PSF		Frequency	# of Subjects	Charge	DIRECTS, subtotal	Dept.CRA10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
					$ 80,284.31	$ 8,028.43	$ 88,312.74	$ 22,961.31	**$ 111,274.05**
Pharmacy Cost Center - other services NCA	**$ 5,600.00**				$ -	$ -	$ -	$ -	$ -
Pharmacy dispensing - study drug IV	V2, V3, V5, V7, V9	5	10	$ 40.00	$ 2,000.00	$ 200.00	$ 2,200.00	$ 572.00	$ 2,772.00
Pharmacy dispensing - study drug#2	V2-V10	9	10	$ 40.00	$ 3,600.00	$ 360.00	$ 3,960.00	$ 1,029.60	$ 4,989.60
Medical Center Cost Center - patient care NCA	**$ 5,544.31**				$ -	$ -	$ -	$ -	$ -
Blood draw & urine collection for send out to central lab via Med. Ctr. Clin. Labs at 400 Parnassus (36415, 81050)	V1, V4, V6, V8, V10, V11, SFw12, SFw24, SFw36, SFw48, EOS	11	10	$ 16.76	$ 1,843.11	$ 184.31	$ 2,027.42	$ 527.13	$ 2,554.54
Premeds - (from Scott Fields)	V2-V10	9	10	$ 16.53	$ 1,487.70	$ 148.77	$ 1,636.47	$ 425.48	$ 2,061.95
ECGs - performed in GCRC, interpretation in cardiology.	1xV1, 2xV2(+tracing) & 2xV9 +tracing	5	10	$ 44.27	$ 2,213.50	$ 221.35	$ 2,434.85	$ 633.06	$ 3,067.91
CTSI CRS Cost Center - patient care NCA	**$ 25,390.00**				$ -	$ -	$ -	$ -	$ -
Blood draw for send out to central lab	V2, V3, V5, V7, V9	5	10		$ -	$ -	$ -	$ -	$ -
2 infusion visits, 3.5 hours	V2, V3	2	10	$ 404.00	$ 8,080.00	$ 808.00	$ 8,888.00	$ 2,310.88	$ 11,198.88
3 infusion visits, 5 hours	V5, V7, V9	3	10	$ 577.00	$ 17,310.00	$ 1,731.00	$ 19,041.00	$ 4,950.66	$ 23,991.66
					$ -	$ -	$ -	$ -	$ -
Insight Imaging Cost Center	**$ 40,000.00**				$ -	$ -	$ -	$ -	$ -
MRI scans @SFMRC - brain, w/ & w/o contrast	V2, V5, V7, V11	4	10	########	$ 40,000.00	$ 4,000.00	$ 44,000.00	$ 11,440.00	$ 55,440.00
Patient transportation expenses	**$ 3,750.00**				$ -	$ -	$ -	$ -	$ -
reimbursed with receipt up to $25/visit	all visits after screening	15	10	$ 25.00	$ 3,750.00	$ 375.00	$ 4,125.00	$ 1,072.50	$ 5,197.50
					$ -	$ -	$ -	$ -	$ -
					$ -	$ -	$ -	$ -	$ -
					$ -	$ -	$ -	$ -	$ -
					$ -	$ -	$ -	$ -	$ -

Variable Events not included in the PSF and invoiced to Sponsor as they occur	Frequency	# of Subjects	Charge	DIRECTS, subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	TOTAL
				$ 198,484.47	$ 19,848.45	$ 218,332.92	$ 56,766.56	**$ 275,099.48**
Unscheduled visit (w/o MRI)	1	20	1,321.07	$ 26,421.36	$ 2,642.14	$ 29,063.49	$ 7,556.51	$ 36,620.00
Unscheduled visit (w/MRI)	1	20	2,800.00	$ 56,000.00	$ 5,600.00	$ 61,600.00	$ 16,016.00	$ 77,616.00
				$ -	$ -	$ -	$ -	$ -
Blood Draw (exploratory biomarkers)	1	10	180.38	$ 1,803.75	$ 180.38	$ 1,984.13	$ 515.87	$ 2,500.00
Delayed Dose Visit	1	8	2,551.23	$ 20,409.81	$ 2,040.98	$ 22,450.79	$ 5,837.21	$ 28,288.00
Extended B cell monitoring	8	5	1,321.07	$ 52,842.71	$ 5,284.27	$ 58,126.98	$ 15,113.02	$ 73,240.00
Early withdrawl	1	8	3,246.75	$ 25,974.03	$ 2,597.40	$ 28,571.43	$ 7,428.57	$ 36,000.00
Dummy MRI	1	1	1,082.25	$ 1,082.25	$ 108.23	$ 1,190.48	$ 309.52	$ 1,500.00
sreen failures, up to 3	1	3	1,896.10	$ 5,688.31	$ 568.83	$ 6,257.14	$ 1,626.86	$ 7,884.00
				$ -	$ -	$ -	$ -	$ -
				$ -	$ -	$ -	$ -	$ -
				$ -	$ -	$ -	$ -	$ -
				$ -	$ -	$ -	$ -	$ -

Standard Protocol Related Events		Frequency	Charge	DIRECTS, subtotal	Dept.CRA 10%	Directs, Dept	Indirects	Total
Pharmacy annual maintenance fee		2	########	$ 2,000.00	$ 200.00	$ 2,200.00	$ 572.00	$ 2,772.00
Pharmacy close-out fee	*collected in the start-up*		$ 500.00	$ -	$ -	$ -	$ -	$ -
NCRA rebudgeting fee		1	$ 900.00	$ 900.00	$ 90.00	$ 990.00	$ 257.40	$ 1,247.40
IRB full committee review fee		2	########	$ 2,200.00	$ 220.00	$ 2,420.00	$ 629.20	$ 3,049.20
IRB amendment fee		2	$ 541.13	$ 1,082.25	$ 108.23	$ 1,190.48	$ 309.52	$ 1,500.00
storage, long term, off-site $158/box		10	$ 158.00	$ 1,580.00	$ 158.00	$ 1,738.00	$ 451.88	$ 2,189.88
				$ -	$ -	$ -	$ -	$ -
				$ -	$ -	$ -	$ -	$ -
SAE submission fee (per onsite submission)	*estimated and added into per*	2	$ 250.00	$ 500.00	$ 50.00	$ 550.00	$ 143.00	$ 693.00
MedWatch/IND report fee (per repor	*visit payments*		$ 75.00	$ -	$ -	$ -	$ -	$ -

PRINCIPAL INVESTIGATOR	Joe Smith, MD, PhD
SPONSOR	Big Pharma
PROTOCOL NO.	989876XMA
PI INITIATED?	No
START DATE	11/1/11
END DATE	10/31/14
PATIENT TOTAL	10
ACCRUAL RATE	2 per month
PROJECT TITLE	A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Study Drug In Comparison To Standard of Care Drug In Patients With Serious Disease

YEARS	MONTHS
3.00	36.00

PERSONNEL SUMMARY, Direct Costs		
Joe Smith, MD, PhD	Investigator	117,279
	co-inv	818
	co-inv	-
	co-inv	-
	postdoc fellow	-
Amy Smith	Nurse	-
Judy Smith	CRC	125,556
Gene Smith	staff	41,232
	staff	-
	staff	-
	staff	-
	total	284,885

Salary Breakdown

	Name	Role	Months		Fringe rate	Effort	Base	Salary	Fringe	Total
FY12	7/1/11-9/30/11	Role	Months			Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		26.00%	20.00%	170,000	-	-	-
		co-inv	Fringe		26.00%			-	-	-
		co-inv	Fringe		26.00%			-	-	-
		co-inv	Fringe		26.00%			-	-	-
		postdoc fellow	Fringe		23.00%			-	-	-
	Amy Smith	Nurse	Fringe		34.00%		138,560	-	-	-
	Judy Smith	CRC	Fringe		34.00%	65.00%	44,850	-	-	-
	Gene Smith	staff	Fringe		34.00%	10.00%	95,736	-	-	-
		staff	Fringe		34.00%			-	-	-
		staff	Fringe		34.00%			-	-	-
		staff	Fringe		34.00%			-	-	-
								-	-	-
	10/1/11-6/30/12	Role	Months	9.0		Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		26.00%	20.00%	170,000	22,666.67	5,893.33	28,560.00
		co-inv	Fringe		26.00%		-	-	-	-
		co-inv	Fringe		26.00%		-	-	-	-
		co-inv	Fringe		26.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		34.00%		144,102	-	-	-
	Judy Smith	CRC	Fringe		34.00%	65.00%	44,850	19,435.10	6,607.94	26,043.04
	Gene Smith	staff	Fringe		34.00%	10.00%	95,736	6,382.40	2,170.02	8,552.42
		staff	Fringe		34.00%		-	-	-	-
		staff	Fringe		34.00%		-	-	-	-
		staff	Fringe		34.00%		-	-	-	-
								48,484.17	14,671.28	63,155.46
							fiscal year subtotal	48,484.17	14,671.28	63,155.46
FY13	7/1/12-9/30/12	Role	Months	3.0		Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		29.00%	20.00%	178,500	8,925.00	2,588.25	11,513.25
		co-inv	Fringe		29.00%		-	-	-	-
		co-inv	Fringe		29.00%		-	-	-	-
		co-inv	Fringe		29.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		37.00%		144,102	-	-	-
	Judy Smith	CRC	Fringe		37.00%	65.00%	44,850	7,288.16	2,696.62	9,984.78
	Gene Smith	staff	Fringe		37.00%	10.00%	95,736	2,393.40	885.56	3,278.96
		staff	Fringe		37.00%		-	-	-	-
		staff	Fringe		37.00%		-	-	-	-
		staff	Fringe		37.00%		-	-	-	-
								18,606.56	6,170.43	24,776.99
	10/1/12-6/30/13	Role	Months	9.0		Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		29.00%	20.00%	178,500	26,775.00	7,764.75	34,539.75
		co-inv	Fringe		29.00%		-	-	-	-
		co-inv	Fringe		29.00%		-	-	-	-
		co-inv	Fringe		29.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		37.00%		149,866	-	-	-
	Judy Smith	CRC	Fringe		37.00%	65.00%	46,644	22,739.07	8,413.46	31,152.53
	Gene Smith	staff	Fringe		37.00%	10.00%	99,565	7,467.41	2,762.94	10,230.35
		staff	Fringe		37.00%		-	-	-	-
		staff	Fringe		37.00%		-	-	-	-
		staff	Fringe		37.00%		-	-	-	-
								56,981.48	18,941.15	75,922.63
							fiscal year subtotal	75,588.04	25,111.58	100,699.62
FY14	7/1/13-9/30/13	Role	Months	3.0		Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		31.00%	20.00%	187,425	9,371.25	2,905.09	12,276.34
		co-inv	Fringe		31.00%		-	-	-	-
		co-inv	Fringe		31.00%		-	-	-	-
		co-inv	Fringe		31.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		39.00%		149,866	-	-	-
	Judy Smith	CRC	Fringe		39.00%	65.00%	46,644	7,579.69	2,956.58	10,535.77
	Gene Smith	staff	Fringe		39.00%	10.00%	99,565	2,489.14	970.76	3,459.90
		staff	Fringe		39.00%		-	-	-	-
		staff	Fringe		39.00%		-	-	-	-
		staff	Fringe		39.00%		-	-	-	-
								19,440.08	6,831.93	26,272.01
	10/1/13-6/30/14	Role	Months	9.0		Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		31.00%	20.00%	187,425	21,866.25	6,778.54	28,644.79
		co-inv	Fringe		31.00%	2.00%	187,425	624.75	193.67	818.42
		co-inv	Fringe		31.00%		-	-	-	-
		co-inv	Fringe		31.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		39.00%		155,861	-	-	-
	Judy Smith	CRC	Fringe		39.00%	65.00%	48,510	23,648.63	9,222.97	32,871.60
	Gene Smith	staff	Fringe		39.00%	10.00%	103,548	7,766.10	3,028.78	10,794.89
		staff	Fringe		39.00%		-	-	-	-
		staff	Fringe		39.00%		-	-	-	-
		staff	Fringe		39.00%		-	-	-	-
								53,905.74	19,223.96	73,129.70
							fiscal year subtotal	73,345.82	26,055.89	99,401.70
FY15	7/1/14-9/30/14	Role	Months	3.0		Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		33.00%	2.00%	196,796	983.98	324.71	1,308.70
		co-inv	Fringe		33.00%		196,796	-	-	-
		co-inv	Fringe		33.00%		-	-	-	-
		co-inv	Fringe		33.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		41.00%		155,861	-	-	-
	Judy Smith	CRC	Fringe		41.00%	65.00%	48,510	7,882.88	3,231.98	11,114.86
	Gene Smith	staff	Fringe		41.00%	10.00%	103,548	2,588.70	1,061.37	3,650.07
		staff	Fringe		41.00%		-	-	-	-
		staff	Fringe		41.00%		-	-	-	-
		staff	Fringe		41.00%		-	-	-	-
								11,455.56	4,618.06	16,073.62
	10/1/14-6/30/15	Role	Months	1.0		Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		33.00%	2.00%	196,796	327.99	108.24	436.23
		co-inv	Fringe		33.00%		196,796	-	-	-
		co-inv	Fringe		33.00%		-	-	-	-
		co-inv	Fringe		33.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		41.00%		162,095	-	-	-
	Judy Smith	CRC	Fringe		41.00%	65.00%	50,450	2,732.73	1,120.42	3,853.15
	Gene Smith	staff	Fringe		41.00%	10.00%	107,690	897.42	367.94	1,265.36
		staff	Fringe		41.00%		-	-	-	-
		staff	Fringe		41.00%		-	-	-	-
		staff	Fringe		41.00%		-	-	-	-
								3,958.14	1,596.60	5,554.74
							fiscal year subtotal	15,413.70	6,214.66	21,628.36
FY16	7/1/15-9/30/15	Role	Months			Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		35.00%	2.00%	206,636	-	-	-
		co-inv	Fringe		35.00%		206,636	-	-	-
		co-inv	Fringe		35.00%		-	-	-	-
		co-inv	Fringe		35.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		43.00%		162,095	-	-	-
	Judy Smith	CRC	Fringe		43.00%	65.00%	50,450	-	-	-
	Gene Smith	staff	Fringe		43.00%	10.00%	107,690	-	-	-
		staff	Fringe		43.00%		-	-	-	-
		staff	Fringe		43.00%		-	-	-	-
		staff	Fringe		43.00%		-	-	-	-
								-	-	-
	10/1/15-6/30/16	Role	Months			Effort	Base	Salary	Fringe	Total
	Joe Smith, MD, PhD	Investigator	Fringe		35.00%	2.00%	206,636	-	-	-
		co-inv	Fringe		35.00%		206,636	-	-	-
		co-inv	Fringe		35.00%		-	-	-	-
		co-inv	Fringe		35.00%		-	-	-	-
		postdoc fellow	Fringe		23.00%		-	-	-	-
	Amy Smith	Nurse	Fringe		43.00%		168,579	-	-	-
	Judy Smith	CRC	Fringe		43.00%	65.00%	52,468	-	-	-
	Gene Smith	staff	Fringe		43.00%	10.00%	111,998	-	-	-
		staff	Fringe		43.00%		-	-	-	-
		staff	Fringe		43.00%		-	-	-	-
		staff	Fringe		43.00%		-	-	-	-
								-	-	-
							fiscal year subtotal	-	-	-
							Totals	212,831.73	72,053.41	284,885.14

Summary

Personnel	FY12	FY13	FY14	FY15	FY16	FY17	FY18	DIRECT TOTALS
Salaries	48,484.17	75,588.04	73,345.82	15,413.70	-	-	-	212,831.73
Benefits	14,671.28	25,111.58	26,055.89	6,214.66	-	-	-	72,053.41
								-
Computing/Data Processing	633.38	950.08	970.08	256.69	-	-		2,810.22
								-
								-
Supplies	25.00	25.00	25.00	25.00				100.00
								-
								-
								-
								-
								-
								-
Other Expenses								-
GAEL insurance, escalating	281.21	483.76	513.42	107.90	-	-	-	1,386.29
Desktop Support, ITS	266.00	399.00	399.00	107.80	-	-		1,171.80
								-
Rent off-campus buildings, $10191.6/5 per month is $2,036.32	11,618.42							11,618.42
								-
CTMS annual fee - TBD								-
								-
								-
								-
								-
								-
	75,979.47	102,557.46	101,309.20	22,125.75	-	-	-	**301,971.88**
							NCRA 10% Total	30,197.19
							Dept. Total	332,169.07
							Indirect Costs, Total	86,363.96
							Total Budget	418,533.02

Salary Escalation Guidelines
5% faculty increases each July 1st.
4% fellow increases each July 1st.
4% staff increases each October 1st.
Fringe increases in fiscal years, FY12 - FY17
If the fringe rate for a particular employee is higher than the standard guidelines, actual fringe rates will be applied in calculations.

Budget Notes

Standard Budget Calculations
ITS desktop recharge calculated as ($33*%effort per mo.)
Dept. computer support calculated as ($83.34*%effort per mo.)

PRINCIPAL INVESTIGATOR	Joe Smith, MD, PhD
SPONSOR	Big Pharma
PROTOCOL NO.	989976XMA
PI INITIATED?	No
START DATE	11/1/11 MONTHS 3.00
PROJECT TITLE	A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Study Drug In Comparison To Standard of Care Drug In Patients With Serious Disease

Salary Breakdown

PI

	Role	Months: 3.0	Effort	Base	Salary	Benefits	Total
Joe Smith, MD, PhD	Investigator	Fringe: 26.00%	5.00%	170,000	2,125.00	552.50	2,677.50
	co-inv	Fringe: 26.00%		-	-	-	-
	co-inv	Fringe: 26.00%		-	-	-	-
	co-inv	Fringe: 26.00%		-	-	-	-
	postdoc fello	Fringe: 23.00%		-	-	-	-
Amy Smith	Nurse	Fringe: 34.00%	1.00%	138,560	346.40	117.78	464.17
Judy Smith	CRC	Fringe: 34.00%	14.50%	44,850	1,625.82	552.78	2,178.60
Gene Smith	staff	Fringe: 34.00%	2.00%	95,736	478.68	162.75	641.43
	staff	Fringe: 34.00%		-	-	-	-
	staff	Fringe: 34.00%		-	-	-	-
	staff	Fringe: 34.00%		-	-	-	-
					4,575.90	1,385.81	5,961.71
Supplies							6.87
Computing/Data Processing							56.25
Other Expenses							
General, Automobile & Employee Liability insurance@$0.58 per $100 of wages							26.54
Desktop Support, ITS							23.63
CHR initial review fee							2,200.00
Pharmacy Set-up fee, uncomplicated							3,198.00
Pharmacy close-out fee							500.00
CTSI CRS start-up fee is $1,500 if needed, add							1,500.00
Off-campus rent for 3 months ($75/month)							225.00
Patient Payment Cards							
						Study Team Direct Cost Total	**13,698.00**

Central Admi

	Role	Months: 3.0	Effort	Base	Salary	Benefits	Total
Budget Analyst	Analyst	Fringe: 34.00%	6.60%	92,700	1,529.55	520.05	2,049.60
		Fringe: 34.00%			-	-	-
		Fringe: 34.00%			-	-	-
		Fringe: 34.00%			-	-	-
		Fringe: 34.00%			-	-	-
		Fringe: 34.00%			-	-	-
		Fringe: 34.00%			-	-	-
		Fringe: 34.00%			-	-	-
		Fringe: 34.00%			-	-	-
					1,529.55	520.05	2,049.60
Supplies							118.10
Computing/Data Processing							16.50
Other Expenses							
General, Automobile & Employee Liability insurance@$0.58 per $100 of wages							8.87
Desktop Support, ITS							6.93
						NCRA Preaward Direct Cost Total	**2,200.00**
						NCRA 10%	**1,589.80**
						Dept. Total Direct Costs Start-up	**17,487.80**
						Indirect Cost Total	4,546.83
						Grand Total Due from Sponsor	**22,034.62**

Standard Budget Calculations
Computing/Data Processing support calculated as 3 months*$83.34*sum(all% effort)
ITS desktop recharge calculated as 3 months*$35*sum(all%effort)

Budget Notes		
	study team	6,300.00

PRINCIPAL INVESTIGATOR	Joe Smith, MD, PhD		
SPONSOR	Big Pharma		
SPONSOR PROTOCOL NO.	989976XMA		
PI INITIATED?	No		
CONTRACT START DATE	11/1/11	YEARS	MONTHS
CONTRACT END DATE	10/31/14	3.00	36.00
NUMBER OF SUBJECTS	10		
SUBJECT ACCRUAL RATE	2 per month		
PROJECT TITLE	A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Study Drug In Comparison To Standard of Care Drug In Patients With Serious Disease		

Comments to Postaward	INDIRECT RATE	26.0%
	Dept.CRA	$ 61,863.86
	PI	594,438.65
	Dept. Total Directs	$656,302.52
	Total Indirects	$ 170,638.65
	Total Award	$826,941.17

First Payment $23,534.62

	DIRECTS, subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
Nonrefundable Start-up Fees (not included in the PSF)	$ 16,980.25	$ 1,698.02	$ 18,678.27	$ 4,856.35	**$ 23,534.62**
Investigator's Team Budget	$ 6,300.00	$ 630.00	$ 6,930.00	$ 1,801.80	$ 8,731.79
Preaward proposal preparation fee	$ 2,200.00	$ 220.00	$ 2,420.00	$ 629.20	$ 3,049.20
IRB review fee	$ 2,200.00	$ 220.00	$ 2,420.00	$ 629.20	$ 3,049.20
CTSI review fee	$ 1,500.00	$ 150.00	$ 1,650.00	$ 429.00	$ 2,079.00
Pharmacy start-up and close out fees	$ 3,698.00	$ 369.80	$ 4,067.80	$ 1,057.63	$ 5,125.43
MRI dummy run fee	$ 1,082.25	$ 108.23	$ 1,190.48	$ 309.52	$ 1,500.00
		$ -	$ -	$ -	$ -
		$ -	$ -	$ -	$ -
		$ -	$ -	$ -	$ -

	DIRECTS, subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
Refundable Start-up Prepayments	$ -	$ -	$ -	$ -	$ -
Patient Payment Cards	$ -	$ -	$ -	$ -	$ -
Enrollment of X number of subjects		$ -	$ -	$ -	$ -

Total Payments from Visits	# of subjects	SPONSOR PAYMENT per subject	# of visits	PAYMENT per visit	subtotal per subject	Dept.CRA 10%	Indirects	PAYMENT per subject
Multiple arms, but they are the same rate	10	$ 52,980.71	16	NA, visits vary in $	$ 38,225.62	$ 3,822.56	$ 10,932.53	$ 52,980.71
						$ -	$ -	$ -
						$ -	$ -	$ -
						$ -	$ -	$ -
						$ -	$ -	$ -
						$ -	$ -	$ -

Groups providing services to subject visits	Labor directs per visit	# of visits	DIRECTS,subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
Joe Smith, MD, PhD			$ 301,971.88	$ 30,197.19	$ 332,169.07	$ 86,363.96	$ 418,533.02
			$ 301,971.88	$ 30,197.19	$ 332,169.07	$ 86,363.96	$ 418,533.02
				$ -	$ -	$ -	$ -

Services included in the PSF		Frequency	# of Subjects	Charge	DIRECTS, subtotal	Dept.CRA10%	Dept. Total Directs	Indirects	SPONSOR PAYMENT
Pharmacy Cost Center - other services NCA	**$ 5,600.00**				$ -	$ -	$ -	$ -	$ -
Pharmacy dispensing - study drug IV	V2, V3, V5, V7, V9	5	10	$ 40.00	$ 2,000.00	$ 200.00	$ 2,200.00	$ 572.00	$ 2,772.00
Pharmacy dispensing - study drug#2	V2-V10	9	10	$ 40.00	$ 3,600.00	$ 360.00	$ 3,960.00	$ 1,029.60	$ 4,989.60
Medical Center Cost Center - patient care NCA	**$ 5,544.31**				$ -	$ -	$ -	$ -	$ -
Blood draw & urine collection for send out to central lab via Med. Ctr. Clin. Labs at 400 Parnassus (36415, 81050)	V1, V4, V6, V8, V10, V11, SFw12, SFw24, SFw36, SFw48, EOS	11	10	$ 16.76	$ 1,843.11	$ 184.31	$ 2,027.42	$ 527.13	$ 2,554.54
Premeds - (from Scott Fields)	V2-V10	9	10	$ 16.53	$ 1,487.70	$ 148.77	$ 1,636.47	$ 425.48	$ 2,061.95
ECGs - performed in GCRC, interpretation in cardiology	1xV1, 2xV2(+tracing) & 2xV9 +tracing	5	10	$ 44.27	$ 2,213.50	$ 221.35	$ 2,434.85	$ 633.06	$ 3,067.91
UCTSI CRS Cost Center - patient care NCA	**$ 25,390.00**				$ -	$ -	$ -	$ -	$ -
Blood draw for send out to central lab.	V2, V3, V5, V7, V9	5	10		$ -	$ -	$ -	$ -	$ -
2 infusion visits, 3.5 hours	V2, V3	2	10	$ 404.00	$ 8,080.00	$ 808.00	$ 8,888.00	$ 2,310.88	$ 11,198.88
3 infusion visits, 5 hours	V5, V7, V9	3	10	$ 577.00	$ 17,310.00	$ 1,731.00	$ 19,041.00	$ 4,950.66	$ 23,991.66
					$ -	$ -	$ -	$ -	$ -
Insight Imaging Cost Center	**$ 40,000.00**				$ -	$ -	$ -	$ -	$ -
MRI scans @SFMRC - brain, w/ & w/o contrast	V2, V5, V7, V11	4	10	########	$ 40,000.00	$ 4,000.00	$ 44,000.00	$ 11,440.00	$ 55,440.00
Patient transportation expenses	**$ 3,750.00**				$ -	$ -	$ -	$ -	$ -
reimbursed with receipt up to $25/visit	all visits after screening	15	10	$ 25.00	$ 3,750.00	$ 375.00	$ 4,125.00	$ 1,072.50	$ 5,197.50
					$ -	$ -	$ -	$ -	$ -
					$ -	$ -	$ -	$ -	$ -
					$ -	$ -	$ -	$ -	$ -
					$ -	$ -	$ -	$ -	$ -

Variable Events not included in the PSF and invoiced to Sponsor as they occur	Frequency	# of Subjects	Charge	DIRECTS, subtotal	Dept.CRA 10%	Dept. Total Directs	Indirects	TOTAL
				$ 198,484.47	$ 19,848.45	$ 218,332.92	$ 56,766.56	**$ 275,099.48**
Unscheduled visit (w/o MRI)	1	20	1,321.07	$ 26,421.36	$ 2,642.14	$ 29,063.49	$ 7,556.51	$ 36,620.00
Unscheduled visit (w/MRI)	1	20	2,800.00	$ 56,000.00	$ 5,600.00	$ 61,600.00	$ 16,016.00	$ 77,616.00
				$ -	$ -	$ -	$ -	$ -
Blood Draw (exploratory biomarkers)	1	10	180.38	$ 1,803.75	$ 180.38	$ 1,984.13	$ 515.87	$ 2,500.00
Delayed Dose Visit	1	8	2,551.23	$ 20,409.81	$ 2,040.98	$ 22,450.79	$ 5,837.21	$ 28,288.00
Extended B cell monitoring	8	5	1,321.07	$ 52,842.71	$ 5,284.27	$ 58,126.98	$ 15,113.02	$ 73,240.00
Early withdrawl	1	8	3,246.75	$ 25,974.03	$ 2,597.40	$ 28,571.43	$ 7,428.57	$ 36,000.00
Dummy MRI	1	1	1,082.25	$ 1,082.25	$ 108.23	$ 1,190.48	$ 309.52	$ 1,500.00
sreen failures, up to 3	1	3	1,896.10	$ 5,688.31	$ 568.83	$ 6,257.14	$ 1,626.86	$ 7,884.00
				$ -	$ -	$ -	$ -	$ -
				$ -	$ -	$ -	$ -	$ -
				$ -	$ -	$ -	$ -	$ -
				$ -	$ -	$ -	$ -	$ -

Standard Protocol Related Events	Frequency	Charge	DIRECTS, subtotal	Dept.CRA 10%	Directs, Dept	Indirects	Total
Pharmacy annual maintenance fee	2	########	$ 2,000.00	$ 200.00	$ 2,200.00	$ 572.00	$ 2,772.00
Pharmacy close-out fee *collected in the start-up*		$ 500.00	$ -	$ -	$ -	$ -	$ -
NCRA rebudgeting fee	1	$ 900.00	$ 900.00	$ 90.00	$ 990.00	$ 257.40	$ 1,247.40
IRB full committee review fee	2	########	$ 2,200.00	$ 220.00	$ 2,420.00	$ 629.20	$ 3,049.20
IRB amendment fee	2	$ 541.13	$ 1,082.25	$ 108.23	$ 1,190.48	$ 309.52	$ 1,500.00
storage, long term, off-site $158/box	10	$ 158.00	$ 1,580.00	$ 158.00	$ 1,738.00	$ 451.88	$ 2,189.88
			$ -	$ -	$ -	$ -	$ -
			$ -	$ -	$ -	$ -	$ -
SAE submission fee (per onsite submission)	2	$ 250.00	$ 500.00	$ 50.00	$ 550.00	$ 143.00	$ 693.00
MedWatch/IND report fee (per repor *estimated and added into per visit payments*		*$ 75.00*	$ -	$ -	$ -	$ -	$ -

Please provide the following information to produce a first draft of a clinical research project budget.

Project Title

A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Study Drug In Comparison To Standard of Care Drug In Patients With Serious Disease

Primary sponsor	Big Pharma
Sponsor protocol number	989976XMA
Budget negotiation contact	Jane Smith
phone & email	Jane.Smith@bigpharma.com
Contract negotiation contact (if different)	
phone & email	
Anticipated or actual CHR approval date	11/1/11
Type of disease	serious disase
Phase and/or intent of study	phase 3
Anticipated complications:	

Protocol Complexity Rating (subjective)

Low, Medium, or High	High

Name personnel paid from the award	**Role**	Estimated **% Effort** and/or	Estimated **Project Hours**
Joe Smith, MD, PhD	Principal Investigator	0.2	
	co-inv		
	co-inv		
	co-inv		
	postdoc fellow		
Amy Smith	Nurse	0.2	
Judy Smith	CRC	0.6175	
Gene Smith	staff	0.1	
	staff		
	staff		
	staff		
Comments:			

Project Periods

Enter the estimated date when all deliverables will be submitted to the Sponsor	10/31/14
Estimated number of UCSF subjects	10
Estimated subject accrual rate	2 per month
Length of time a subject is expected to participate	146 weeks
Comments:	

Financial Information

Is this an Investigator initiated project?	No		
List all addresses where research is conducted	350 Parnassus and then Mission Bay in Spring 2012		
Will this contract require subcontracts to other sites?	No	If yes, provide # of sites, accrual/site, & site name (if known) in comments box.	
Will this contract require inpatient hospital services?	GCRC infusions	If yes, where?	
Will any part of this project be billed to insurance?	No		
per subject dollar figure or total budget targets, if any	54,554		
Comments:	All the blinding requires additional labor on the budget and increases the complexity.		

Process expectations:	
NCRA Preaward Analyst	*compiles information submitted by the PI (or designee) into a standard, budget template *returns a first draft budget to the PI for review within 5 business days *negotiates a budget and payment terms with the Sponsor, if requested
Principal Investigator	*submits a budget requisition with another meaningful document representing the scope of work (AKA the protocol) *provides required proposal documents to the NCRA as they become available *may negotiate a budget and payment terms with a Sponsor and, when doing so, is acting as an agent of the University and must follow University contracting policies

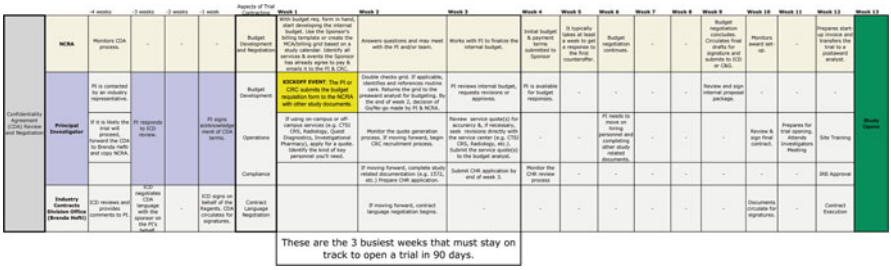
Checklist for submitting required, electronic documents to the assigned, preaward analyst

Informed Consent (ICF)*		submit the most current version
Protocol*		submit the most current version
CHR application**		submit when the final is available
Sponsor's contract		submit when a draft is available
Sponsor's budget and payment terms		submit when a draft is available
CTSI CRS services quote		(if utilized)
Pharmacy services quote		(if utilized)
List other documents that impact the budget		(and submit these documents as they become available)

*If the protocol and/or ICF is not written yet, note this and identify big expense items, such as scans, lumbar punctures, etc. in financial comments on the budget requisition spreadsheet.

**If a contract amendment is triggered from changes to a protocol, submit the summary of changes from the CHR application to the preaward analyst.

Send a message to the budgeting team in the box below regarding time sensitivity, unusual circumstances or items, etc.



Off-site Storage Fees Assessment for Clinical Trials Budgeting

Source Reference:
http://www.campuslifeservices.ucsf.edu/distribution/storage/storage_rates/

<u>Cost Development Assumptions</u>
10 boxes
15 years

Storage fees for Start-up Costs	Rate	Units	Cost
Std. file box per month	$ 0.54	1800	$ 972.00
Warehouse service hourly rate	$ 54.46	8	$ 435.68
Records destruction per box	$ 3.23	10	$ 32.30
Driver delivery charge	$ 70.00	2	$ 140.00
			$ 1,579.98

Direct Cost Std. Charge $ 1,579.98 $ 158.00 per box

<u>Notes</u>
electronic files can be about 5 boxes
paper files can be about 10 boxes
big trials can be 20 boxes

REVISED 9/9/11 via phone call. Rates are no longer listed on web page.

STUDY CALENDAR

Protocol Activity	Screening	Baseline	D1C1	D14C1	Day 1, add'l cycles	Scans	EOT	Off Treatment Follow-up Visit	Follow-ups

Appendix C: Participant Screening/Enrollment/ Withdrawal Log

Date of screening	ICD[a] on file? Y/N	Was participant given a copy of the ICD?[b] Y/N	Was participant enrolled? Y/N. If yes, note date	If no, what was the reason?	Participant ID #	Early withdrawal from research participation? Y/N If yes: 1. Note reason 2. Did participant undergo study termination visit?

[a]Informed consent document (ICD)
[b]If "no" note reason

Appendix D: Site Personnel Signature Log

Study IRB #:_____

Study Title:_____

Principal Investigator: _____

Name	Title/role (PI, coordinator, etc.)	Signature	Initials

Page ____of_____

Appendix E: The SMOG Readability Formula

Step 1: Take the entire text to be assessed.
Step 2: Count 10 sentences in a row near the beginning, 10 in the middle, and 10 in the end for a total of 30 sentences.
Step 3: Count every word with three or more syllables in each group of sentences, even if the same word appears more than once.
Step 4: Calculate the square root of the number arrived at in Step 3 and round it off to nearest 10.
Step 5: Add 3 to the figure arrived at in Step 4 to know the SMOG Grade, i.e., the reading grade that a person must have reached if he is to understand fully the text assessed.

$$\text{SMOG grade} = 3 + \text{Square Root of Polysyllable Count}$$

The SMOG formula is considered appropriate for secondary age (fourth grade to college level) readers.

The premises of McLaughlin's SMOG formula are:

1. A sentence is defined as a string of words punctuated with a period, an exclamation mark, or a question mark.
2. Consider long sentences with a semi-colon as two sentences.
3. Words with hyphen are considered as a single word.
4. Proper nouns, if polysyllabic should be counted.
5. Numbers that are written should be counted. If written in numeric form, they should be pronounced to determine if they are polysyllabic.
6. Abbreviations should be read as though unabbreviated to determine if they are polysyllabic. However, abbreviations should be avoided unless commonly known.
7. If the text being graded is shorter than 30 sentences, follow the steps below:
   i. Count all the polysyllabic words in the text.
   ii. Count the number of sentences in the text.
   iii. Divide the figures obtained in (i) by the figure obtained in (ii) to arrive at average polysyllabic words per sentence.
   iv. Multiply the figure obtained in (iii) with the average number of sentences short of 30.
   v. Add the figure obtained in (iv) to the total number of polysyllabic words.
   vi. Compare the number of polysyllabic words in the SMOG conversion table.

SMOG conversion table	
Total polysyllabic word count	Approximate grade level (+1.5 grades)
1–6	5
7–12	6
13–20	7
21–30	8
31–42	9
43–56	10
57–72	11
73–90	12
91–110	13
111–132	14
133–156	15
157–182	16
183–210	17
211–240	18

SMOG Readability Calculator
http://www.readabilityformulas.com/free-readability-formula-tests.php

Appendix F: Subject Visit Tracking Log

Study IRB #:_____

Study Title:_____

Principal Investigator:_____

Subject Study ID #		Visit #__ Date	Visit #___ Date	Visit #__ Date	Visit #__ Date	Date Final study visit	Date and reason if early termination (please initial)
Example #001	Projected:		2/01/12	3/02/12	4/05/12	5/05/12	
	Actual:	1/10/12	2/01/12	3/06/12			
	Projected:						
	Actual:						
	Projected:						
	Actual:						
	Projected:						
	Actual:						
	Projected:						
	Actual:						
	Projected:						
	Actual:						
	Projected:						
	Actual:						

Page _____of_____

Appendix G: Training Log

This log is designed to be study specific. You may customize this log to be the training record for an individual in the study team.

Name of individual	Training (manual of operating procedures, standard operating procedures, study initiation visit, etc.)	Date of training	Initials of supervisor/PI

Glossary

Adverse reaction (AE) This is a side effect for an adverse reaction or an unanticipated or undesired effect of the experimental therapy. Adverse reactions may be further classified as routine adverse reactions and serious adverse reactions. Serious adverse reactions or serious adverse events may have specific reporting requirement time frames.

Amendment This is a change in the protocol that requires IRB approval prior to implementation. Studies may have several amendments, and these all require IRB approval, and they should be placed in the investigators brochure.

Bias This is a subjective impartiality which may affect the validity of the scientific results of the study. Bias may be controlled by factors such as randomization, blinding, and avoidance of conflict of interest.

Blinded Blinding occurs when one or more parties involved in a clinical trial are unaware of whether they are receiving treatment, placebo, or a control medication or intervention. Parties involved in blinding may comprise subjects, those dispensing medication, and those evaluating subjects, including investigators.

Case-control study This is a type of scientific trial that compares two cohorts. One cohort may have a disease (such as skin cancer) and be compared to a similar that does not have the disease. The study may for example examine the levels of exposure to carcinogens such as arsenic in each group up prior to the appearance of the disease to determine potential causality.

Case report form (CRF) This form is used to enter data related to protocol study procedures. CRFs may be paper or electronic (eCRFs). The latter have become more popular for a number of reasons, including real-time gathering and assessment of data. Case report forms are unique to each subject and the principal investigators responsible for maintaining the accuracy of the data in case report forms. In the case of a review by a sponsors monitor or an audit by regulatory agency, the accuracy of the data will be verified comparing CRF information with source documentation.

Collaborative IRB training initiative (CITI) This is a portal for certifying all levels of clinical research training including GCP (good clinical practices) training.

A. Nasir (ed.), *Clinical Dermatology Trials 101: A Primer for Dermatologists*,
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Code of federal regulations (CFR) These are the permanent rules and regulations published in the Federal Register by government agencies. Also known as administrative law, they contain sections and parts which govern human subjects' research.

Clinical research associate (CRA) or CCRA (certified clinical research associate) This individual is often referred to as the monitor. The clinical research associate is typically employed by the sponsor to monitor clinical trial. The CRA makes sure that all trials were conducted according to the protocol and within guidelines mandated by GCP or the ICH.

Clinical research coordinator (CRC) This individual is also known as the study coordinator. The study coordinator typically administers the clinical trial at the investigative site. The study coordinator may be responsible for the collection of all documents related to the study and distribution of supplies at the investigative site.

Clinical trial Human subjects' clinical trials are also known as clinical studies. These trials are designed to test a drug, medical device, or a biologic in a small population to determine whether its use can be considered safe and effective for a wider general population.

Community-based clinical trial (CBCT) This is a clinical trial typically conducted in a private practice setting as opposed to a large academic medical center.

Contract research organization (CRO) This is an agency contracted by a sponsor such as a pharmaceutical company to oversee clinical research at investigative sites.

Control group This is a group of human subjects to which the investigative intervention is compared. The control group may receive a placebo or may receive an established standard therapy for their disease.

Controlled trials This is a type of trial in which two groups are compared. The control group is either given standard therapy for disease or placebo and another group is given the experimental therapy.

Crossover trial This is a type of study in which all human subjects participating in the study receive both interventions: placebo and investigational product. At a point in time defined by the protocol, the control group receives the intervention and the intervention group receives placebo.

Data safety monitoring board (DSMB) This is an independent committee comprised of the board of experts that review clinical trial while it is in progress. The purpose of the data safety monitoring board is to ensure that subjects are not exposed to untoward risk. A data safety monitoring board may suspend a study early if there are concerns about human subjects' safety or if the goals of the trial have been successfully demonstrated.

Data safety monitoring plan (DSMP) This is a plan designed to make certain that clinical trials have appropriate oversight and monitoring of their conduct. The purpose of a data safety monitoring plan is to ensure the safety of human subjects and to ensure the integrity and validity of trial data.

Declaration of Helsinki This is a manifesto published in the 18th world medical assembly in Helsinki, Finland in 1964. The Declaration of Helsinki covers

ethics of biomedical research involving human subjects. Key principles of the declaration of Helsinki to ensure human subjects safety include documentation of valid informed consent and review by an ethics committee.

Demographic data These key features are characteristics of study groups which are pertinent to clinical trial study findings and include items such as gender, ethnic origin, age, medical history, family history, and social history such as occupation or smoking history of participants.

Deviation This is an isolated departure from an IRB protocol and tends to be unintentional. It is often identified retrospectively, after an event has occurred.

Device Devices are used to diagnose or treat or prevent disease and do not achieve their action through chemical means or by altering metabolic function in the human body. Devices maybe tools, apparatus, machines, contrivances, implants, or reagents.

Diagnostic trial These are clinical trials designed to discover more effective or efficient diagnostic tests for a particular disease.

Double-blind study In these studies, their participants nor investigators, Borst and his staff know which human subjects are receiving investigational therapy or which are receiving placebo or standard therapy.

Efficacy This is the ability of therapy or intervention to produce a beneficial result for a human subject. The degree of benefit is defined by the protocol, and the validity of efficacy is defined by statistical criteria.

Eligibility criteria These are criteria defined in the protocol, such as inclusion criteria and exclusion criteria, to allow investigators to determine which screened volunteers may participate in the study.

Endpoint This is the final outcome mentioned in the protocol which the study is attempting to evaluate.

Exclusion/inclusion criteria These are demographic and clinical criteria which determine whether the subject maybe eligible to participate in the clinical trial or maybe excluded from such participation. Typical inclusion and exclusion criteria may include subject age, gender, pregnancy status, presence or degree of disease, prior treatments, concurrent medical therapies, and confounding medical conditions.

Food and Drug Administration (FDA) This is a branch of the Department of Health and Human Services in the United States and is primarily responsible for protecting the public by ensuring the safety and efficacy of all Biologics drugs vaccines medical devices and in safeguarding nation's blood supply.

FDA form 1571 This form tabulates the commitments required by the study sponsor for drug or biologic therapy.

FDA form 1572 This form numerates the commitments and conduct required by the principal investigator performing a drug or biologic study.

Good clinical practices (GCP) These are internationally recognized standards for the ethical conduct of research involving human subjects. The chief aims of GCP standards are twofold: to protect human safety, and to ensure data integrity.

Good laboratory practices (GLP) These are internationally recognized rules for ensuring the quality, integrity, and reliability of data from non-clinical safety studies.

Good manufacturing practices (GMP) These are internationally recognized rules for the manufacture of pharmaceuticals or food products that meet high quality standards and do not pose a hazard to consumers or the public.

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) This legislation is establishing standards in the United States for electronic healthcare transactions and it gives national identifiers for healthcare providers, health plans, and employers. The purpose of the act is to regulate and ensure the security and privacy of health data.

Human subject Also known as a participant or a volunteer or a patient, the human subject is an individual participating and a clinical research trial.

Hypothesis Theory is being tested in a clinical investigation.

Informed consent This is a verification of a human subject's willingness to participate in a clinical trial. Informed consent involves more than a document, rather, it is a process of ensuring that the investigator subject is fully informed of all potential risks and benefits of participating more/not participating in the clinical trial. Participation in clinical trials is strictly voluntary and maybe withdrawn at any time and this should be explicitly discussed during the informed consent process. Informed consent is not static. It may change as new information develops during the course of the trial.

Informed consent document (ICF) Also known as the informed consent form (ICF), this is a document. By the sponsor as part of the protocol is provided to investigators and subjects for discussion and verification of the informed consent process. He informed that the consent document must describe the types of human subjects participating in the trial, have specific information about the study such as its purpose blank and interventions required during the study. It should contain contacts of key individuals involved in the study as well as the risks and potential benefits of participating in the trial. If subjects agree to the contents of the informed consent and the discussion they will be asked to sign the document. Subjects must know that participation in the trial is voluntary and subjects may withdraw at any time without any penalty or loss of benefit rights to which they are entitled.

Institutional Review Board (IRB) This is an oversight committee which reviews clinical trials to make sure that they are conducted in an ethical manner which protects the rights of participating human subjects. The Board consists of a committee of community members, researchers, statisticians, and physicians. In addition to being responsible for determining whether a trial may be approved, institutional review boards also have a responsibility to periodically review research, for example on an annual basis, to ensure that the rights of human subjects during the course of the study are protected.

Intent to treat This is a trial data analysis which includes results from study participants even if they did not receive treatment.

International Conference on Harmonization (ICH) A consortium which has developed global standards on the conduct of clinical research involving human subjects. The purpose of the ICH is to meet or exceed standards in all member nations to allow subject safety, data integrity, and data validity to be streamlined and to prevent inefficiencies and duplications across study sites.

Investigational device exemption (IDE) This permits an approved investigational device to be used in a clinical trial to collect safety and efficacy data. An approved IDE allows a device to be legally shipped to sites conducting investigations without violating other laws under the Food, Drug, and Cosmetic Act (FD&C Act) which prohibits commercial distribution of unapproved devices.

Investigational new drug (IND) This is an application submitted to the FDA requesting permission for human subject testing of a new biologic, antibiotic, drug, or application of a biologic product used for in vitro diagnostic purposes.

Investigator's brochure This is a compilation of all pertinent clinical and non-clinical data compiled in a trial of a drug biological or device at the study site by the principal investigator.

In vivo This is testing in living organisms such as animals, or human subjects.

In vitro This is testing outside of living organisms such as a test tube, petri dish, tissue culture, or organ culture.

Joint Commission on Accreditation of Healthcare Organizations (JCAHO) This is a non-profit US-based organization that accredits and certifies healthcare organizations. It is governed by a 28-member board which includes physicians, nurses, healthcare consumers, medical directors, labor representatives, ethicists, educators, and employers.

Meta-analysis This is a statistical analysis derived from pooled data of similar studies to measure an effect which might be difficult to measure from the results of a single study. The purpose of meta-analysis is often to generate new hypotheses for further studies.

Multicenter trial This is a clinical trial with a single protocol which is conducted at multiple sites with multiple independent investigators. Multicenter trials may occur in one country or maybe worldwide.

National Institutes of Health (NIH) This is one of 11 agencies of the Department of Health and Human Services which is responsible for finding basic science clinical research and conducting studies including the funding of multicenter national clinical studies.

National Cancer Institute (NCI) This is one of 11 agencies of the Department of Health and Human Services charged with cancer research and training.

New drug application (NDA) This is a petition submitted by a sponsor to the FDA for market approval of a new drug designed for human use in interstate commerce in the United States.

Observational study This is a trial which does not involve any intervention or therapy. In studies, disease processes are allowed to be involved actually, and statistical analyses are used to determine whether characteristics separating one group from another are related in any way to health outcomes. Examples of observational studies include case-control studies and cohort studies. One study for example compared the diet history of hospitalized patients with melanoma to hospitalized cancer patients without.

Off label use This is the practice of using a drug device for a condition other than that which is approved by the FDA.

Office for human research protections (OHRP) Under the umbrella of the Department of Health and Human Services, the OHRP is involved in protecting the rights, welfare, and wellbeing of human subjects involved in research supported by DHHS. It is also involved in compliance oversight, and regulatory oversight human clinical studies.

Open label trial This is a clinical trial in which investigators and subjects are aware of the treatment or intervention at the time it is being given.

Orphan drugs These are therapies designed to treat rare diseases. When the sponsor or manufacturer is given an orphan drug status for investigational product, he receives special incentives to bring its therapy to market.

Outcomes study This is a type of trial that assesses the effects of a medication or intervention on study subjects. Interventions may include drugs or treatments with devices, and outcomes may include changes and extent of disease, patient morbidity, or mortality.

P **value** This is a statistical value which represents the probability of the null hypothesis being true. Standard value of P-value < 0.05 means that the probability of the null hypothesis being true is less than 5 %.

Parallel study A parallel study evaluates the results of an intervention on two distinct populations of patients.

Pharmacology This is the discipline studying the effects of drugs on living tissues and organisms. Pharmacology studies how drugs interact with biological processes to lead to a change in function.

Pharmacodynamics (PD) This is a study of the relationship between the concentration of a drug at its site of action, and its effects.

Pharmacokinetics (PK) This is a study of the time course of drug or vaccine absorption, distribution, metabolism, and excretion and a cell, tissue, or living organism.

Pharmacovigilance This is an evidence-based process of assessing the effects of a medication, biological product, alternative medicine product, and traditional medicine product after market approval. Information on adverse effects is collected from healthcare providers and patients in the community. Collated data are then scrutinized for hazards and the information is disseminated to prevent further harm to patients. Sometimes phamacovigilance results in withdrawal of an approved medication if it is determined that continued use presents a serious hazard to the public.

Phase 0 clinical trial This is a study where there is human exposure to minute doses of study drug, with no expected therapeutic goal. Examples of phase 0 trials include microdosing trials and screening trials.

Phase 1 clinical trial This trial often involves a small number of patients around 20–80 and is also called a dosing study. In phase 1 trials, volunteers may be healthy or may have a disease that is being targeted by the therapy. A phase 1 clinical trial typically evaluates different routes of administration of an intervention, timing of doses, as well as safety.

Phase 2 clinical trial This phase of clinical research assesses safety and efficacy. In phase 2 trials, a significant proportion of the study population contains a disease of interest for which the therapy is being used. Phase 2 clinical trials are slightly larger than phase 1 clinical studies and may involve 100–300 subjects.

Phase 3 clinical trial These are larger clinical trials encompassing 1,000–3,000 subjects or more and may be carried out at multiple institutions or clinics in one country or globally. Phase three clinical trials typically compare a new intervention to the standard of care and assess safety efficacy and adverse events.

Phase 4 clinical trial These are trials conducted after market approval and are used to refine understanding of therapy including its risks, benefits, and ideal use.

Pivotal study This is typically a phase 3 clinical study which contains the data used by regulatory agencies such as the FDA when making a decision for marketing approval. Pivotal studies tend to have excellent controls, randomization, and tend to be double blinded.

Placebo This is an inert or inactive treatment which has no pharmacologic therapeutic value. It is given as a sham intervention in order to compare its effects to the experimental therapy.

Placebo-controlled study In this type of study, there are two groups of subjects: one group is administered a sham intervention (placebo), the other group is given an active drug or therapy. The two groups are compared to see if the active drug is more effective than the placebo.

Placebo effect This is a favorable physical or psychological outcome of a sham intervention that occurs outside of any special property of the inert substance or interactive therapy given. The placebo effect may occur because of expectations of improvement by the subject, or by the investigative team.

Preclinical studies These are studies performed in the laboratory either in vitro or in animals before a drug or device is tested in human subjects.

Prevention trials These are trials conducted to prevent the appearance of the disease and subjects who are healthy to prevent the recurrence of the disease and subjects who are in remission. Interventions in prevention trials may consist of pharmacologic therapies, alternative medicine, vaccines, or lifestyle changes. An example would be a prospective trial looking at the effects of sunscreen use on the prevention of skin cancer.

Principal investigator (PI) This is the individual and investigative site responsible for the conduct of a clinical trial according to the protocol and according to good clinical practices. If there are number of clinicians (sub-investigators or sub-Is) at a particular site, the investigator who is the leader of the team would be called the principal investigator.

Prospective study This is a trial in which study subjects receiving treatment or intervention is assessed over time to evaluate their outcomes according to criteria or endpoints delineated in the protocol.

Protected health information (PHI) This is an individually identifiable health information, including demographic information, relating to a subject's physical or mental health. PHI needs to be de-identified if it is to be disclosed electronically without violating HIPAA. Identifiers such as names, geographic location, dates, and social security numbers.

Protocol This is the template upon which a clinical trial is based. The protocol establishes a rationale for a particular study and is designed with the primary focus being the protection of the health and safety and ethical rights of human subjects. Protocol is designed to answer a specific research question and does so with a clear description of the type of study being conducted, all study procedures, all medications and devices, all doses, inclusion and exclusion criteria for all subjects, details regarding informed consent, study end points, and the duration of the study.

Quality assurance (QA) This is the practice of ensuring optimal quality of product in pharmaceutical development through SOPs and practices which address every stage of the process from resource acquisition, to product manufacture and delivery.

Quality control (QC) This is the practice of testing sample batches of product in pharmaceutical development and comparing them to the desired or optimal specification.

Randomization This is a statistical method of assigning study subjects into different treatment groups in order to eliminate selection bias.

Randomized trial This is a trial in which study subjects are assigned by random chance to one or more treatment arms of a clinical trial. This allows investigators to test different treatments in similar subject populations.

Report of prior investigations (ROPI) This is included in all IDE submissions and contains relevant literature surveying all prior clinical, animal, and laboratory testing of the device.

Retrospective study In these trials, subjects have already been treated and their data are selected from experiences and outcomes that they have had in the past. Retrospective studies are often plagued with bias because investigators can select patient populations with known outcomes.

Screening trial These are clinical trials designed to test methodologies for the diagnosis of a disease.

Side effects These are harmful undesired effects and investigational drug or device. Drugs and devices must be evaluated for immediate, short-term, and long-term side effects.

Serious adverse event (SAE) This is any study related event which can result in death, a life-threatening situation, hospitalization, or prolonged hospitalization disability incapacity or congenital defect in study subjects or their offspring.

Single blind study In this type of trial, participants are unaware of the intervention or drugs they are receiving, while the investigator or the investigative team is aware.

Source documentation This is the first place where data are recorded. Source documents can be original data, certified copies of data or observations, or any other information necessary, Henry constructing and evaluating the events occurring during the conduct of the study.

Sponsor This is an individual, group, or organization that funds and manages a clinical trial. To avoid conflict of interest, the sponsor may not directly conduct the investigation.

Standard operating procedures (SOP) These are specific written instructions for the management conduct of a clinical trial and are designed to ensure consistency and efficiency.

Statistical significance This is the probability that observed difference occurred by chance alone. And in clinical trials, statistical significance is dependent on the size of the population studied, as well as the size of the differences being measured.

Statistician An expert in statistics. And in most trials, statisticians play a key role in the early stages of design of trial. On going statistical methodology can make the difference between a successful and an unsuccessful trial. Furthermore, one of the principles of ethics of conducting a clinical trial is to minimize harm to subjects in society and to maximize benefit. Statisticians play a central role in determining optimal participant size in a clinical trial.

Study endpoint This is a clinical outcome point designed to assess the safety or efficacy of an intervention.

Surrogate endpoint This is a biomarker or some other substitute for a clinical endpoint. A surrogate endpoint should have demonstrated validity in predicting a clinical endpoint.

Suspended This is when a study has stopped recruiting participants early, but may start doing so again in the future.

Terminated This is when a clinical trial has ended early and is not starting again. Subjects are not offered further study-related examinations or therapies.

Toxicity This is an adverse effect caused by a therapy which is harmful to the participant's health. Toxicity may be related to the active investigational product as well as the health of the participant. Depending on the severity of the disease being studied, a certain level of toxicity may be acceptable.

Withdrawn This is a type of recruitment status, indicating that a clinical trial has ended before enrolling any participant.

Index

A. Nasir (ed.), *Clinical Dermatology Trials 101: A Primer for Dermatologists*,
DOI 10.1007/978-3-319-09027-6

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