Human Medical Research

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Editors

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Ethical, Legal and Socio-Cultural Aspects

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Part I
Historical and Socio-Cultural Contexts in Medical Research

Chapter 2
British Responses to Nazi Medical War Crimes

Fiona McClenaghan

2.1 Introduction

The British response to Nazi medical war crimes has not been as extensively studied as that of the Americans; this is largely due to the fact that Britain did not decide to utilise the results of Nazi research to the same extent as its ally (Hunt 1985). However, Britain did undertake a similar policy of scientific exploitation in post-war Germany. The first priority of the British government was to ensure that intellectual reparations from Nazi science could be secured (Farquharson 1997). Yet, as it became increasingly apparent that Nazi science had used human subjects for inhumane experimentation, the government was faced with the dilemma of whether to exploit or condemn German science.

These apparently contradictory aims could not be easily resolved. Britain was facing bankruptcy. By the Treasury's own estimate, at least a quarter of the nation's wealth had been consumed by the war effort and more money was needed to reconvert British industry to peacetime, to offset war-time disinvestment and to repair the physical damage of war (Kirby 2006). Therefore, securing intellectual reparations from German science, so preeminent before the war, was a priority (Proctor 1995). However, this economic drive to secure the best Nazi scientists for exploitation soon became political as tensions mounted at the outset of the Cold War. Suspicion of the Russians led the government to demand that all useful scientists be exploited by Britain to avoid them falling into Soviet hands (Longden 2009). This fierce competition served to undermine the efforts of British war crimes investigators to highlight the illegality of some of the Nazi research.

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Illegality, however, was also a problem. Although experimentation on humans, often leading to death or deformity, was shocking to the British war crimes investigators, it was not in itself a war crime. There was no precedent in international law for such acts. Therefore, even if the British government had the will and the financial means to be able to prosecute Nazi doctors, it was far from clear who should have conducted such a trial and on what legal premise (Sherriff Bassiouni et al. 1973). As survivors of human experimentation began to mobilise at the end of the war with the help of the British war crimes investigators, it was clear that not to prosecute would undermine British moral superiority as victors. However, not to exploit German science was economically and politically unacceptable. Therefore, a dual policy of prosecution and exploitation was worked out (Weindling 2004).

2.2 Allied Expectations

Germany was the world leader in the fields of life, physical and social sciences before the Nazi takeover in 1933 (Proctor 1995). The Allies assumed that with such a great scientific infrastructure the Germans would have made significant scientific discoveries during the war, especially in the sciences directly related to chemical and biological warfare. It was this scientific knowledge which the Allies were keen to accept as "intellectual reparations" for the war. Farquharson has argued that these intellectual reparations were, in fact, more valuable than any economic reparations, as their exact monetary worth could not be easily quantified, and so more could be gained than would have otherwise been condoned (Farquharson 1997). However, the expected highly sophisticated German war effort was not realised and it became increasingly obvious that the ethical basis of German science had been sacrificed to the principles of racial hygiene and its promotion of "experimentation without limit" (Lifton 1986). How the policies of the British government changed in response to the gradual realisation of the extent of Nazi scientific abuses tells us much about the agenda of Britain in post-war Germany.

2.3 Exploitation

The main medical experimental camps of Ravensbruck and Auschwitz were liberated by the Soviets, and Dachau by the Americans. The prosecution of medical war criminals was not an obvious priority, nor even a long term aim, for the British government. Its aims for German science in the wake of the war were two fold. Firstly, to impose appropriate restraints on German scientific research to ensure that Germany could never again become powerful enough to threaten Europe. Secondly, to exploit its wartime scientific achievements (TNA: PRO CAB 124/544 1945).

After a war which had been so costly to Britain, both humanly and economically, there was a fear that if Germany were allowed to continue scientific research, especially in the field of chemical and nuclear weapons, it could again become the aggressor of Europe (TNA: PRO CAB 124/544 1945). The fear of rearmament prompted the Cabinet to propose a prohibition of research which could be linked in any way to military aims by closing any research establishments that could not be adapted to non-military research. However, there was allowance made for those research institutions which were "necessary for the exploitation of German science" to remain open (TNA: PRO CAB 124/544 1945).

In 1944, an Anglo-American interrogation and internment camp, code named "Dustbin", was opened for German scientists. The camp was run by the Enemy Personnel Exploitation Section (EPES), part of the British wing of the Anglo-American-French Field Information Agency (Technical) (FIAT), but situated in the American Zone as the number of scientists being held in the British zone had already exceeded the limit allowed (Weindling 2004). Although designed for only 90 scientists, by September 1945, more than 5,000 scientists and their families inhabited the crowded camp. The British were so keen that no one else should get hold of any valuable scientist that a list was compiled of 15,000 names, with an average of 500 more being added each week (Longden 2009).

There were more German scientists in British custody than the British could cope with, largely because many had chosen to flee west from Berlin to avoid the Red Army (Weindling 2004). As the situation at Dustbin grew ever more acute, the Americans threatened to release all the scientists and the British were forced to produce an accurate estimate of how many scientists were of significant exploitative value (Londgen 2009). They estimated that there were approximately 500 scientists in British custody that might be a "serious danger in the hands of a potentially hostile power" (TNA: PRO FO 1031/65), but even these were too many to be employed either in Britain or the British zone. Importantly, the hostile power referred to here was not Germany but Russia. There was an air of desperation about British policy at the outset of the Cold War.

> We must evacuate [the scientists] to Britain, whether they are willing to go or not. (TNA: PRO FO 1031/65)

It was the interrogations at Dustbin which would illuminate to the British the true extent of Nazi human medical research. The key figure was Captain John Thompson, a Royal Canadian Air Force intelligence officer attached to the RAF. His interrogation of Fritz Klein, a Nazi doctor who had worked in Auschwitz before being transferred to Belsen just a few weeks before the liberation in June 1945, would prove to be the key to establishing the role of concentration camp doctors. Klein admitted to experimenting with psychotropic drugs and making daily selections for the gas chambers (Weindling 2004).

This was the first realisation by the British of the power wielded by doctors in the concentration camps. Klein's admission was to prove crucial because it increased the interest of the British investigators on the ground in Germany in medical atrocities. Thompson's success was rewarded with a promotion to Chief of

the Scientific Branch of the British FIAT in October 1945. However, his new role, which was to make the results of German scientific and medical research available to the British and not to prosecute Nazi scientists involved in unethical research, illustrates that at the end of 1945, the primary focus of British policy remained exploitation (Weindling 2004). Nevertheless, Thompson used his new role to delve deeper into the conduct of doctors involved in medical research in the camps (Lifton 1986).

The men being interrogated at Dustbin were not lawyers or politicians but scientists, and this greatly aided the British investigators. Many of their statements were thinly veiled attempts at self-exoneration; for example, the opening statement of Ranke, a physiologist involved in carbon monoxide testing:

> I did not initiate or permit the initiation of any class of experiment which may have the slightest effect on individual well-being. (TNA: PRO FO 1031/76 1945)

The majority of the scientists shocked their interrogators with their candour; Major E.B. Gill was astonished that,

> […] a good deal of the information was gratuitous and came from the elaboration of simple questions. (TNA: PRO FO 935/56 1945)

By May 1946, when nearly 30,000 reports on scientists at Dustbin had been completed, the extent of human experimentation had become apparent. However, doubts remained over whether medical atrocities actually constituted war crimes and, more pressingly, what to do with those suspected of being involved in unethical research being held in British custody (TNA: PRO FD1/5826 1945). While interrogations were going on at Dustbin, there was still no British policy for dealing with the perpetrators of medical atrocities. With no list of wanted doctors, no centralised collection of evidence and no intention of ever holding a Doctors' Trial, interrogators did not know what to do with the evidence they were obtaining (TNA: PRO WO 309/374 1945).

The scope of the investigations at concentration camps was huge because thousands of inmates were willing to testify against Nazi doctors. The report goes on to state that:

> […] investigation could be carried on indefinitely provided that there is sufficient [resource] to carry it on. (TNA: PRO WO 309/374 1945)

Such resources were not about to be willingly provided for the investigation of war crimes committed against anyone except British citizens. Dustbin was costing a huge amount of money to keep open, but there were clear economic gains to be had from interrogating and exploiting leading scientists (Weindling 2004). In contrast, the moral gains to be had from interviewing survivors of medical experimentation were not tangible enough for the British government to take an interest, and significant pressure had to be put on the government to make it change its view.

2.4 The Dual Policy

Thompson, in a memo to the United States Judge Advocate in late 1945, pointed out the problem:

> In the course of investigating research work done in Germany in the medical and allied sciences, a deeply disturbing problem has come to light… in many, and probably all, German universities and research institutes the use of humans as subjects was thought desirable… [if our sample is representative then] one is able to say that the practice was universal throughout Germany. (TNA: PRO FO 1031/74 1946a, b)

Thompson was aware that a decision had to be made whether to prosecute doctors for their crimes, and pressure would have to be exerted on the Allied governments to force a decision. He warned that to prosecute would necessitate putting aside a large amount of human and economic resources and so should only be undertaken if it could be done adequately, but it was his view that the "ominous consequences" that could arise in the future as a result of a failure to act on so serious an issue more than necessitated the expense. Thompson proposed a meeting of medical and legal authorities on an inter-Allied basis to discuss the best course of action on the matter (TNA: PRO FO 1031/74 1946a, b).

Permission from the War Office for this meeting did not arrive until five months later, and in the meantime, Thompson's comments continued to cause a stir in London. He estimated that "something like 90% of the members of the medical profession at the highest level were involved in one way or another". This huge estimate led the Foreign Office to dismiss his claim as a "gross exaggeration". It felt that any investigation to "detect further crimes of this nature would be undesirable and unproductive" and, perhaps more importantly in the economic climate of the time, expensive (TNA: PRO FO 937/165 1945).

The British government was concerned not only about the cost of the investigations themselves, but also future costs which would be incurred if Thompson's estimate was accurate and a large number of doctors would have to be removed from their posts, making Germany further dependant on the Allies for medical care. The British government did not feel so ethically responsible for prosecuting the perpetrators of medical atrocities that it was willing to spend any of its (admittedly tight) budget on doing so. The point which was raised again and again was that neither the victims nor the perpetrators of the experiments were British, and so Britain had no responsibility to prosecute. This added weight to the economic argument (Weindling 2004).

Nevertheless, Thompson's estimate did make an impact and a compromise position between trying to find every criminal doctor in Germany and being seen to condone their actions by doing nothing was beginning to be seriously considered. The British War Crimes Executive in Nuremberg in late-1945 proposed that a policy may be acceptable:

> […] where victims are German or stateless persons is to bring one or two conspicuous cases before [British] military government courts leaving others to be dealt with before German courts with (initially) British observer. (TNA: PRO FO 1031/74 1946a, b)

Therefore, by December 1945, the British finally began to formulate a plan to prosecute Nazi doctors, but the proposal only included those who could be described as war criminals. "Many more have acted unethically but do not come into the war crimes category" and there would be no attempt to prosecute this huge group (TNA: PRO FO 1031/74 1946a, b).

This proposal was essentially a dual policy to both exploit and prosecute German science. Weindling has argued that the policy was hypocritical and showed that the British were more focused on the "application than [the] misapplication of medical expertise" (Weindling 2004). However, Schmidt has contested this black and white view, arguing that the moral dilemma between exploitation and prosecution is largely retrospective (Schmidt 2006). He argues that the exploitation of Nazi scientific achievements was an acceptable substitution for war reparations. There was a moral dilemma among the investigators on the ground and this is reflected by their determination to continue gathering evidence, beyond their brief, for the crimes about which the victims testified. However, the British government, due to its financial constraints, was unable either to limit exploitation or to increase funds for prosecution. A compromise was the best option available.

2.5 Trying to Unite the Allies

Thompson had been aware from late-1945 that there was sufficient evidence to prosecute a number of leading Nazi doctors. However, he was concerned that, after the International Military Tribunal (IMT) of the major Nazi leaders was completed, the zeal to prosecute Nazi doctors would wane and the economic concerns of the British government would prevail to diminish the size and scope of a Doctors' Trial (Weindling 2004). On 15 May 1946, a medico-legal meeting of the British, American and French arms of FIAT took place. The meeting asserted that FIAT was "purely confined to the economic, technical and scientific exploitation of Germany", its raison d'être from before the end of the war, "but that in view of the obtrusion of this matter into the results of this exploitation" a meeting should be called to discuss the matter (TNA: PRO WO 309/471 1946a, b, c).

The British laid out their approach:

> The investigation of these experiments in connection with what went on in concentration camps rather than the direct approach to the commission of the crimes themselves. (TNA: PRO WO 309/471 1946a, b, c).

The Russians were conspicuous by their absence; no Soviet delegate had been invited. The primary concern for the French was for an international moral condemnation of Nazi medicine to be made as soon as possible, even before trials were undertaken. Britain and the US were, above all else, keen to avoid committing to another four power commission that could culminate in a four power

doctors' trial, in the mould of the IMT, which would necessitate working with the Russians (Schmidt 2006).

The Americans dominated the conference and suggested that, as an alternative to a "cumbersome" four power trial, each nation should choose a case to investigate and prosecute it in its own zone (TNA: PRO WO 309/471 1946a, b, c). Although the French felt that an IMT would be a fairer way to try Nazi doctors (as did the absent Soviets), they were overruled. Concerns over how zonal trials, which would necessitate great inter-Allied co-operation and evidence exchange, would work in an increasingly tense atmosphere were not raised. Thompson planned for further meetings to be held every two months in an attempt to encourage Allied co-operation (TNA: PRO WO 309/471 1946a, b, c).

The French took the lead in setting up a Scientific Commission for War Crimes by the next meeting on 31 July. Aware that the Cold War was having a significant effect on the discussions of medical war crimes, the French asserted that Russian representatives should be asked to the next meeting and pushed for an International Scientific Commission for War Crimes to be set up on a four power basis (TNA: PRO WO 309/471 1946a, b, c). However, despite the best diplomatic efforts of the French, the informal FIAT meetings had no political power. Permission to set up national commissions or to join international ones had to be gained from governments heavily invested in Cold War animosity.

Characteristically the American government stood firm against joining any commission which could lead to another four power trial. In addition to their Cold War concerns, there was also a worry that great publicity from a medical trial could:

> […] so stir public opinion against the use of humans in any experimental manner whatsoever that a hindrance will thereby result to the progress of science. (TNA: PRO WO 309/471 1946a, b, c)

In appendix "B" of the minutes was enclosed the culmination of these two concerns: the draft by Dr. Ivy, the US War Secretary, of what would become the Nuremberg Code (TNA: PRO WO 309/471 1946a, b, c). The Americans came to realise that if they took on the trial themselves, they would have much greater control of publicity, be able to write an ethical code which would allow human experimentation to continue within set rules and, most importantly, ensure that they did not have to collaborate with the Soviets.

The British government, keen to avoid another burden on its devastated economy, did not object to America taking charge. In August 1946, Brigadier General Telford Taylor's group took responsibility for running the trial, but made it very clear that:

> […] his team had not the facilities for investigation other than of documents and accordingly would have to rely on the investigations carried out by teams at present working in the British and American zones. (TNA: PRO WO 309/471 1946a, b, c)

Schmidt has argued that the great contribution to the trial by the British is too often forgotten in accounts of post-war US policy which claim that the Americans

alone were responsible for the Doctors' Trial (Schmidt 2008). Although the Americans undoubtedly deserve credit for managing to transfer a large amount of legal machinery and personnel to Nuremberg in a short time, the British had already completed the lion's share of the evidence gathering. However, in the light of the economic state of Britain, it is clear that the actions of the British government were not the result of complete disinterest in using the evidence of their own investigators, but rather of economic necessity.

2.6 Legal Problems

Until December 1945, the British had no policy for the prosecution of medical criminals, and so the most pressing issue for the interrogators was to decide whether or not medical crimes against non-Allied personnel were illegal. The phrase "medical war crime" was coined in November 1945 by Thompson in a memo to the US war crimes Judge Advocate (TNA: PRO FO 1031/74 1946a, b). The creation of this term would have great repercussions at the Doctors' Trial. To try someone for a crime which was not illegal at the time it was committed is a post facto law which had then, as now, dubious legality (Taylor 1993). However, even before a medical trial had been contemplated, the lack of legal certainty meant that the interrogation of suspected perpetrators of medical crimes was difficult and the interrogators had to work within unwritten and largely assumed ethical guidelines.

Schmidt has argued that, at the time, it was not certain whether or not it was "ethical" to use scientific data which had been generated under unethical circumstances, or whether using such research could be seen as condoning the research and the researcher (Schmidt 2006). However, it was undoubtedly legal as there was no international law which banned the practice. At the time of the Second World War, the laws of war were defined by The Hague Convention of 1907 and The Geneva Convention of 1864, amended in 1929. Crimes against humanity, although related to war, had no legal basis at this time. Therefore, there was great uncertainty about what to do with the data being acquired from human experimentation.

Schmidt is correct to remind the reader that the ethical standards of today were not enshrined in law in the Allied countries either. In the United States, forced sterilisation had been legal in some states since 1907, something which the eugenicist Ernst Rudin was keen to point out while under house arrest (Weindling 2004). However, the medical crimes of the Nazis had to be compared against some ethical premise and that yardstick was Allied ethics. Therefore, forced sterilisation performed on the German population outside the concentration camps, although the most widespread Nazi crime, would have no part in a Nazi Doctors' Trial conducted by the United States (Sofair and Kaldijian 2000). This admission was a regrettable consequence of the Americans taking control of the Doctors' Trial.

2.7 Conclusion

The response of the British government to Nazi medical war crimes was complex. It was not a simple question of whether the British government cared enough about the Nazi violation of medical ethics to bring the perpetrators to justice. Such a simplistic appraisal denies the obvious constraints placed on the British government by the economic crisis and the growing political tensions at the outset of the Cold War.

One possible light at the end of the tunnel for the British government was the possibility that Germany had made scientific and medical advances during the war. The exploitation of Nazi scientific achievements for the benefit of Britain was seen as a legal, acceptable and even preferable form of war reparations in 1945 (Farquharson 1997). However, the German war machine was certainly not all that it had been expected to be. Despite huge investment in Dustbin and interrogation units, little new information was gleaned. However, in the midst of the search for the top scientists, suspicion of the Soviets was growing.

As the Allies no longer had a common enemy to unite them, their interests diverged and competed. Competition for scientists was so fierce that the British forcibly extradited many German scientists to Britain or held them in Dustbin for as long as possible, to avoid them falling into Soviet hands while encouraging the Americans to do the same (TNA PRO FO 945/904 1945, 1946). It was in this atmosphere of economic woe, desperation and political suspicion that evidence of Nazi human experiments began to be unearthed.

The reports of the British war crimes investigators were key in forcing the British government to look beyond the problems of post-war Britain and realise that, as a victor, it had to, in some form, contribute to bringing the perpetrators of medical crimes to justice. However, how to do this was a problem. With no precedent in international law for such acts, none of the Allied governments knew what to do (Sherriff Bassiouni et al. 1973). An IMT in the model of that for the Nazi leaders was unfavourable to the Americans and the British in the light of the Cold War, but for a long time, none of the powers was willing to step forward to take on the trial. The eventual decision for the Americans to take on the Doctors' Trial was as much about ensuring that they did not have to work with the Soviets and that they could set the precedent for human research after the war, as it was about bringing justice to the victims (TNA: PRO WO 309/471 1946a, b, c). If justice had been their sole aim, then forced sterilisation would have been a prosecutable crime.

The British, in providing the majority of the evidence for the trial, have gone largely unacknowledged in the historiography (Schmidt 2006). However the British government at the time was far from concerned about the history books; the economic issues in Britain were pressing and it wanted to focus on rebuilding its economy. The dual policy of the government appears on the surface to have conflicting aims: How can a government both exploit and prosecute the same activities? Weindling has called the policy hypocritical, (Weindling 2004) however, it would be fairer to see the policy as the farthest Britain could stretch towards prosecution without worsening its domestic situation.

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Chapter 3
History and its Relevance in the Development and Teaching of Research Ethics

Rael D. Strous

3.1 Introduction

It is clear that research ethics play a critical role in ensuring that research in general, and medicine in particular, is performed in a correct and just manner. However, while the concepts and awareness of research ethics are rapidly developing, many would suggest that attentiveness to the principal issues is still lacking and that the development and teaching of research ethics still leave much to be desired in various academic departments, most notably in the basic sciences and in many medical schools around the world (Eisen and Berry 2002; Beresin et al. 2003; Rosenbaum 2003).

It has been argued that investing in the teaching of research ethics is a waste of precious teaching and education resources. Either the individual is ethical and moral in his or her behaviour or he or she is not. Studies among biomedical trainees and postdoctoral fellows have observed that education in research ethics did not necessarily predict significant improvement regarding willingness to engage in misconduct (Kalichman and Friedman 1992; Eastwood et al. 1996; quoted in Eisen and Berry 2002). However, based on historical precedent, it is well known that this is not necessarily the case. The majority of those who have engaged in unethical conduct in research and/or clinical activities are not necessarily "evil". Rather, the vast majority of unethical behaviour emanates from:

> […] ordinary people under ordinary circumstances who make uninformed or poor ethical decisions. (McGuffin 2008).

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It is precisely for this reason that in the teaching of research ethics it is argued that sharing historical examples of unethical practice is critical in ensuring that concepts learned are formulated and engrained in trainees and students (e.g., Reverby 2010; Horner and Minifie 2011; Strous 2011a, b).

3.2 Development of Research Ethics in the Aftermath of the Nazi Era

A prime example of where critical aspects of research ethics were ignored and blatantly disregarded transpired not too long ago during the Nazi era in Germany and other parts of Europe. It is important to note that much of current practice and guidelines in research ethics emanates from this period in the form of the Nuremberg Code of ethics (Markman and Markman 2007) issued over six decades ago. This code is generally accepted to be the initial definitive foundation of research ethics and was formulated in reaction to the profound disregard for human autonomy and justice during the facilitation of human experimentation carried out by Nazi researchers. The Nuremberg Code essentially defined basic rights of research participants and the responsibilities of investigators (Markman and Markman 2007). While the Nuremberg Code was the critical step in bringing research ethics into the frontline of medical ethics and concern for patient and subject welfare, it was only the first step. Many took issue with the Nuremberg Code since it was not legally binding, was considered a response to such an extreme situation that it limited its relevance to general research, focused exclusively on the obligations of the researchers such that it would deter subject participation, and that voluntary consent is demanded at all times, which would potentially exclude the possibility of research in various special populations, such as the mentally-ill and children (Markman and Markman 2007).

In response to some of these issues, as well as other historical currents and misdeeds in medical research, the code has been updated while maintaining the crucial framework of the initial code. This began with the World Medical Association's 1964 Declaration of Helsinki, which emphasized the importance of clinical research in the improvement of human welfare and assisted in the description of the process of ethical research. The problematic Tuskegee Syphilis Study led to a further update in research ethical code with the Belmont Report formulated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979 (originally published in 1978). It was in this report that several key concepts in research ethics were declared, namely respect for persons, beneficence, and justice. Knowledge of the historical process in developing these concepts contributes to sensitivity and optimal internalization of the principles since it provides context and perspective. Thus, in addition to the concepts themselves, how they came about should also be included in the research ethics training process. The National Institute of Health (NIH) in the US appears to be cognisant of this and have more recently introduced facts with some emphasis

from the historical development of research ethics into their ethics training model for human research that all employees and awardees of grant funds are required to undertake. Thus, as an important background to the teaching of research ethics, they include mention of Nazi medical practice and the development of the Nuremberg Code, the Syphilis Study at Tuskegee, the US government 1944–74 Cold War Human Radiation Experiments, the 1963 Jewish Chronic Disease Hospital Study, the 1963–66 Willowbrook Study, and the 1999 death of Jesse Gelsinger (http://phrp.nihtraining.com/users/login.php).

3.3 Teaching of Research Ethics Based on Knowledge of Medicine During the Nazi Era

While many research findings arising from this period are of dubious value and have been termed pseudoscience by some (e.g., Hildebrandt 2009), others do have value and it has been debated whether these research findings should be of any use and quoted in any academic discussion of the subject matter (Schafer 1986; Sheldon et al. 1989). However, what remains in clear and contemporary use are several eponyms. Eponyms are labels of medical disorders associated with individuals who originally described the condition and serve a valuable role in remembering and identifying the disorder. The use of eponyms in medical practice is ubiquitous, however many have argued that in some situations, the change or discarding of such eponyms becomes important on ethical grounds. This situation would arise when research associated with the disorder and individual was carried out under such overtly unethical conditions that it would be wrong to perpetuate, and thus "reward", the memory of the individual after whom the disorder is named (Strous and Edelman 2007).

Several eponyms have been identified with names of individuals who have been linked to explicit crimes of the researchers and the medical community during the Nazi era. Over the past decade or two, there have been an increasing number of calls to adopt alternative medical nomenclature for these conditions (e.g., Shevell 2003; Cubelli and Della Sala 2008). Not all agree with this stance (e.g., Gross 2003), and Seidelman has suggested that the maintenance of these names in the form of eponyms serves an important learning experience in and of itself for research ethics (quoted in Blackwell 2010). In contrast, examples exist of eponyms named after Nazi era victims, eponyms of those who protested such injustices and eponyms of those who had to flee prejudice and death. It has been proposed that these latter eponyms should be remembered and even strengthened as opposed to the former group, which should be abolished (Strous and Edelman 2007). These changes would serve as critical learning experiences in the teaching of research ethics. The reason for this change is based on the consideration that the greatest accolade a medical researcher and physician can earn from colleagues is the honour of an eponym linked to one's name. Therefore, the medical profession should consider removing any respect given to those involved in or associated with

gross ethical transgressions tied to ethical oversight in research or practice. Thus, eponyms remain just one example of how ethics teaching can be enhanced by means of the use of historical examples.

Other learning points exist from this period which are also potential opportunities for discussion and development of ethical awareness and sensitivity. McClenaghan (see Chap. 2, Sect. 2.4), for example, quotes Schmidt, who explored the value of Nazi medical research and reported that beginning in the immediate aftermath of the war, it remained unclear whether or not it was ethical to use scientific data which had been generated under unethical circumstances, or whether using such research could be seen as condoning the research and the researcher (Schmidt 2006). While today there is more clarity regarding how to approach this issue (e.g., Schafer 1986; Sheldon et al. 1989), it remains a fascinating subject for discussion at the level of teaching research ethics to students within the context of group discussion and encouraging participant self-expression and opinions. This is made all the more relevant by noting comments at the time by a key figure, Captain John Thompson, who was a Royal Canadian Air Force intelligence officer and who interrogated several Nazi physicians and scientists in the period after the war. As quoted by McClenaghan, in a memo to the United States Judge Advocate in late 1945, Thompson stated that:

> In the course of investigating research work done in Germany in the medical and allied sciences, a deeply disturbing problem has come to light… in many, and probably all, German universities and research institutes the use of humans as subjects was thought desirable… [if our sample is representative then] one is able to say that the practice was universal throughout Germany. (see McClenaghan Chap. 2, Sect. 2.4)

This is a fascinating indictment of German academia, which in many ways led the world in scientific endeavour and vigour at the time (Proctor 2000)—all the more contributing to the ethical learning experience regarding how this could transpire and what could prevent this ever occurring again, even in a country and milieu of scientific and research excellence.

Reis and Wald (2009) in a pivotal discussion of the use of the Holocaust in the ethics learning experience during medical school state that:

> […] incorporating an understanding of medicine and the Holocaust into the medical curriculum can be a valuable way to encourage future physicians to learn from past events that have transformed biomedical ethics and so inform practice and research. (Reis and Wald 2009).

While this is most certainly the case with the behaviour of physicians during the Nazi era, which serves as the ultimate case study on the subject of unethical medical practice in modern times, the question remains if this profound learning experience may be extended to aspects of the function of physicians during other periods in distant and more recent history. More importantly, the challenge exists whether the abuse of the power inherent in the physician's function over this period can be contrasted in a learning experience with the valour, dignity and bravery of other physicians who managed to function otherwise during this time (Chelouche 2005).

3.4 Teaching of Research Ethics Based on Aspects of History of Medicine

It follows that if we are to implement research ethics on a global scale, it is imperative to learn from where ethical principles have been violated around the world in modern history, and not necessarily limited only to the Nazi era. This is important since many examples exist where, despite codes of medical ethics being available in certain countries, gross violations of these principles have transpired. Physicians in Germany, for example, despite being well aware of the 1931 strict code of medical ethics regarding ethical research and patient treatment, managed to violate the code and facilitate the extreme injustice and unethical behaviour under the guise of doing good for the general community and society (Cohen 2010). Many physicians at the time engaged in unethical behaviour believing that they were doing the right thing from a moral and scientific standpoint (Lifton 1986). Thus, merely learning about ethical principles without any understanding of where physicians have transgressed, despite the existence of these codes, is insufficient.

While the most overt example of this is the case of the German Nazi physicians, other unfortunate well-known examples exist from many countries around the world, including the Soviet Union, Argentina, South Africa, Serbia, and the USA. Thus, when medical trainees are being taught ethical principles, it is important to ensure that they are exposed to what has transpired around the world in various contexts where other physicians have chosen to ignore central ethical principles in clinical and research activity and perform in a manner they have deemed to be acceptable medical practice. This is crucial since, despite best intentions, ethics training and policy without a focus on history may be ineffectual.

I have argued elsewhere that although many believe that ethics training in the context of medical school, residency training or science studies alleviates the possibility that such profound ethical violations may reoccur, unfortunately history has taught us otherwise (Strous 2011b). Despite gross violations of patient's rights and dignity, many physicians in the distant and more recent past maintained that they were acting justly in terms of moral behaviour and furthering the interests of science for society. They often believed that their medical contribution was critical for the furthering of the interests of science and the good of mankind despite blatant disrespect for the value of human life. Thus, ethics training without some emphasis on clinical and research psychiatric practice with examples from history would be essentially amiss.

Within the context of teaching research ethics, many examples from more recent history may be provided which would facilitate this learning process. One systematic and efficient model of including aspects from history in the teaching of medical ethics is by reference to the four cardinal ethical concepts of medical ethics, often referred to as the "Georgetown mantra" (Beauchamp and Childress 1979, 6th ed. 2009). These values, that are frequently quoted in medical ethics debate and discussion, are autonomy, beneficence, nonmaleficence, and justice.

Many make use of these concepts as a model to explain the concept of medical ethics and their importance. In the same manner, it can be suggested that, following a brief explanation of the concepts, examples from history can be discussed with students where these concepts have been ignored or violated (Strous 2011a, b). The illustration of vivid examples of unethical practice from history increases the chances that lessons may be learned and that the concepts will be applied in a more efficient, just and professional manner. Precise examples from history provided can be modified according to the nature of the studies in which the ethical coursework takes place. Thus, for example, medical internists would discuss examples from history regarding where other medical internists have strayed from the path of ethical practice, so too psychiatrists, surgeons, pathologists, neuroscientists, etc. Examples of actual cases have a greater impact than merely learning principles. Ideally this should be facilitated in the context of small groups or case-based learning (Chen 2003). This provides relevance and interest value, thus enhancing the possibility of internalizing the ethical lessons learned. While an approach along these lines is expected to be effective in the teaching of medical ethics given the vast history of the field, this method is not limited to medicine. In fact its utility in ethics education has been well recognized for some time in other fields. The use, for example, of historical analysis in the teaching of ethics in engineering education has also been found to be extremely useful (Billington 2006). Thus, this methodological effectiveness should not be seen as being limited to medicine. Along these lines, it has also been suggested that ethics education should be imparted in interprofessional rather than profession-specific ways. In this way, teaching of research ethics with relevant references to the history of ethical violations in one profession will have relevance for the teaching of ethics in another (Yarborough et al. 2000). Some courses have seen fit to include modules of the general history of medicine in their ethics teaching curriculum (Andre et al. 2003). It is expected that these modules would include aspects of whether members of the profession have strayed from the good moral practice of medicine.

3.5 Relevance of History for the Development of "Ethical Sensitivity" and "Ethical Decision-Making"

While the subject matter of medical ethics in general, and research ethics in particular, is vast, it is critical that the questions are posed. Awareness of the dilemmas is integral to the development of "ethical sensitivity". It is clear what the role of ethical principles and codes of conduct are in ensuring ethical behaviour in the practice of medicine. However, in order to ensure optimal ethical conduct in research despite the knowledge of principles and historical precedent as described above, it is crucial for researchers to develop "ethical sensitivity". This may also be described as the development of "ethical mindfulness" and is characterized by an ability to recognize the issues of ethical relevance (Guillemin et al. 2009). The

tools of research ethics' principles are essential in ethical decision-making rather than adopting tailor-made solutions to every situation and dilemma. It may be argued that this concept of "ethical sensitivity" is close to Aristotle's concept of "phronesis", which may be defined as the development of "practical reasoning", and the demonstration of optimal ethical judgment about wrong and right, irrespective of the prevailing sentiment and what has been taught. This is linked to the development and maturation of the physician's or researcher's character over time and is related to the cultivation of the inherent virtues of the individual. Development and maturation of this characteristic among physicians and researchers would go a long way to ensure that, despite the proliferation of research with rapidly advancing technology in numerous areas, ethical principles have relevance. In a globalized world and the resulting ethical pluralism, bioethics in this manner comes to represent the skill of developing what has been termed "soft ethics expertise", which is expressed and reflected in sensitivity to relevant values (Kovacs 2010).

In addition to learning how and when to identify ethical issues of concern in research, it is also critical to be aware of various core principles. Awareness of and sensitivity to these core concepts are vital in ensuring that research ethical principles are protected on a global scale in places where their priority is less and rather based on social or economic factors. An example of this are philosophical constructs based solely on political factors and considerations which should never be allowed to define research or clinical practice. In addition, in a research context, illness prevention should never be pursued in a single-minded fashion at the expense of illness management. Ethics awareness and sensitivity needs to be maintained, even after formal training, as an enduring aspect of clinical and research practice in the context of continued education. In order to ensure sensitivity to the issues, it is thus important for trainees to discuss ethical dilemmas and develop proficiency in ethics problem-solving throughout the course of training, beginning from day one, as a parallel track of education over their years of study.

Arguably, the development of "ethical sensitivity" is the first and most important step in the acquiring of skills in the process of "ethical decision-making". While it is important to know what the ethical issues in research are, it is just as important to know how to deal with them. Thus, an adequately developed approach to "ethical decision-making" is vital. However, despite basic education in topics of general medical ethics, medical and general science students and residents receive very little guidance in ethical dilemma resolution (e.g., Alfandre and Rhodes 2009). This represents a profound deficiency in an important aspect of training since although identification of the ethical dilemma is an important initial step, a decision on action needs to be made under optimal ethical conditions.

What does the process of ethical decision-making entail? There are several stages. Firstly, the ethical problem needs to be identified. Secondly, various ethical concepts need to be enlisted in debating various solutions to the quandary. Finally, various principles in problem resolution need to be explored (reviewed in Strous 2011a, b). It is important to ensure that there is some degree of peer review and

discussion of the issue at hand and that even once a decision has been made that it is open to be reconsidered.

There are various theoretical approaches to ethical decision-making. One well-known approach which challenges the physician to be aware of precisely which theoretical school of thought he or she is engaging in ethical decision making is that of the World Medical Association (Williams 2005). This scheme distinguishes between "rational" versus "non-rational" approaches to ethical decision-making. Non-rational approaches include obedience, imitation, feeling or desire, intuition, and habit, while rational approaches engage concepts of deontology, consequentialism (utilitarianism), principlism, and virtue ethics. The approach has value since even within a particular theoretical approach there is a place for evaluating factors for and against a particular decision. This method is useful since it engages all, or at least most of, the widely acceptable decision-making theories in medical ethics, is known around the world since it is freely distributed and is applicable to both research and clinical interventions. Its worth is in the fact that it is wide-ranging and serves as a valuable tool in the formal and informal teaching of students from a variety of disciplines in both research and clinical ethics. Students can be challenged to explore all the factors relevant to ethics of any particular situation and, in this manner, consider possible solutions in a well thought out and controlled manner.

3.6 Conclusion

The teaching of research ethics remains a challenge for educators in the field. The quest for innovative approaches continues in order to optimize the learning experience during the limited time available in many medical school and science learning curricula. One important approach is that of the use of history in the teaching of research ethics, as described above. It is believed that discussion of where research in the past has strayed from the path of what we clearly today consider as ethical medical and/or scientific practice would optimize the possibility that such behaviour would never be repeated. While the Nazi medical experience is the prime example in modern times, others exist. The hope is that learning from the past influences the development of ethical sensitivity critical to the pursuit of research under optimal moral conditions. While this may seem intuitive, in order to verify this assumption, empirical research is encouraged to clarify whether this is, in fact, the case. This would include the development of appropriate evidence-based evaluation methods for its effectiveness (Chen 2003). It is proposed that attention to historical aspects of medicine, both positive and negative, will improve the process of ethical decision-making by health-care providers. An openness to identify these issues from the past and explore them as a crucial learning experience, no matter how embarrassing and indicting it may be for the field, is crucial for the future development and maturation of research in general and medicine in particular. With awareness of past mistakes, the practice of medical research must be applied with care and principled purpose to all.

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Chapter 4
Human Embryo Research and Islamic Bioethics: A View from Iran

Mansooreh Saniei

4.1 Introduction

Bioscientific and technological innovations during the last few decades have caused a great impact on society and improved the quality of life. As the unpremeditated use of these scientific developments raises moral issues and can cause serious threat to society, each discipline attaches greater attention to studying and analysing these developments in the light of ethical, social and legal dimensions from different perspectives. Religion, for instance, disseminates information to increase awareness in society in general, and among researchers in particular. However, few scientific or medical issues have been as contested as the issue of human embryo research.[1] The intense controversies are due to the fundamental ethical problems which this kind of research poses. The opponents raise elemental ethical concerns. In most cases, including human embryonic stem cell (hESC) research, the use of embryos for the purpose of research leads to the destruction of the embryo. For the opponents of embryo research, this is tantamount to murder and shows a lack of respect for the

[1] Embryo research is the practice of experimentation on human embryos and stem cells. The investigations are mainly carried out on left-over embryos produced after in vitro fertilisation (IVF). During IVF, a woman's ovaries are stimulated to produce multiple ova which are, in turn, fertilised them by the husband's or a donor's sperm. Some of the healthy embryos produced by this process are implanted into the woman's womb. One or more of them will probably develop into a foetus and be born nine months later. Excess embryos are then frozen in the event that a pregnancy does not develop or the couple wants another baby. Some of these frozen embryos are used by scientists to carry out research. Additionally, aborted embryos can also be used for research (see Østnor 2008).

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dignity of man. On the contrary, the proponents of embryo research hope for the development of an inexhaustible reservoir of cells for the repair of damaged tissue. This could be a new therapeutic approach to cure hitherto incurable diseases, such as Alzheimer's and Parkinson's (Baharvand 2009).

The discussion about human embryo research ultimately boils down to one question: Should a human embryo enjoy the same protection of life and dignity as a born human being? Generally, religious groups have been in the forefront of those speaking out publicly for and/or against embryo research. The conservative Christian view is that human life is created at conception, and embryos should, therefore, be treated as living human beings. They state that no research use of embryos which is not for the benefit of those particular embryos should be allowed. In contrast, the Jewish religion holds that an embryo does not become human until 40 days after conception, and the Muslims reflect that human life begins when the soul enters the developing embryo or foetus, which sometimes occurs weeks or months after conception. This range of views that embryos do not have the potential to produce individual humans until after certain number of days of growth, to the position that they are significant groups of human cells, likely accounts for different levels of acceptance of hESC research: It is supported in the Jewish community, is accepted in many Muslim countries, yet is opposed by the Roman Catholic Church and some Protestant denominations (Guinn 2006).

Although different traditions express different opinions depending on when life begins, research on human embryos has advanced at a tremendous pace during the last three decades. Moreover, hESCs, isolated from embryos, are generally accepted as a source of great potential for human welfare. Nevertheless, we need to address the question of whether human embryos are of such immense moral significance that we should never destroy them, even in research that might treat and perhaps save the lives of human beings. What follows is not a detailed ethical, social and legal report covering all aspects related to embryo issues, but a brief overview of the main arguments of Islamic scholars about embryo research. Firstly, the view of Islamic scholars on the status of the embryo will be presented. To this aim, I shall depict Islam's position on abortion and assisted reproductive technologies (ARTs) and then hESC research. It is helpful to explain the moral controversy surrounding human embryos, particularly hESC research in the Islamic tradition, and to find how Muslims solve their ethical problem in this field of biomedicine. This will also be devoted to an explanation of the scientific and moral-religious position of embryo research, e.g. hESC research in Iran, which has taken the lead among Muslim countries since 2003.

4.2 The Status of the Human Embryo in Islamic Law

The major issue concerning human embryo research, particularly hESC science, is that it mainly results in the destruction of embryos. The question is whether an embryo is considered to be a human person, in which case its destruction

is tantamount to killing? Therefore, what is the status of an embryo in Islamic law (*Shari'a*)? This seems to be best addressed by determining at what point human life begins. According to Seddiqi:

> Human development begins when a sperm cell fuses with an egg cell. This initial fertilized egg, although it is only a single cell, is able to form an entire human being. This cell starts to divide into additional cells, which at this early stage are all able to produce a complete organism. These cells are therefore called totipotent, meaning they have total potential to produce all cell types present in a living human. As development proceeds and an embryo forms, these cells become pluripotent, meaning they have potential to become many different kinds of cells but can no longer give rise to a complete embryo. Later in development, through a process called cell differentiation, these pluripotent cells eventually give rise to the different and more specialized kinds of cells in the body and the different organs begin to form.
> What are stem cells? Stem cells are cells that have not gone through the process of cell differentiation and therefore have the potential to give rise to many different kinds of specialized cells. For instance a stem cell could be used to produce liver cells, brain cells, heart muscle cells, blood cells, etc. The current sources of stem cells include embryos (which, as explained above, consist of pluripotent cells) and fetal tissue. In addition, some recent evidence suggests that even adults have a small number of mulitpotent cells that can be isolated and can later differentiate into various cell types. (Seddiqi 2002:1)

The *Qur'an* describes in a few places the development of the human in the woman's womb, speaking of the breathing-in of the soul, although there is not specific definition of the timing of the beginning of life either the *Qur'an* or *Sunnah* (The habit and usual practice of the Prophet, "Peace be upon Him"). The development of foetus is depicted in the verses:

> We created (*khalaqna*) man of an extraction of clay, then We set him, a drop (*nutfah*) in a safe lodging (i.e. the womb), then We created of the drop a clot (*'alaqah*), then We created of the clot a tissue (*mudghah*), then We created of the tissue bones (*'azm*), then we covered the bones in flesh (*yaksu lahman*); thereafter We produced it as another creature (*khalaqan akhar*). So blessed be God, the Best of creators (*khaliqin*). (The Qur'an 23:12–14)

Based on this passage, the inception of foetal development is graded into three clear stages, including lodging *nutfah* in the women's womb,*'alaqah* and *mudghah*. The *Qur'an* itself does not give any concrete indication as to the exact point in time when the ensoulment occurs. However, it has almost been found in the *hadith* (the sayings of the Prophet, "Peace be upon Him") in the following indication:

> Verily your creation is on this wise. The constituents of one of you are collected for 40 days in his mother's womb; it becomes something that clings ('alaqa) in the same (period) (mithla dhalik), then it becomes a chewed lump of flesh (mudgha) in the same (period) (mithla dhalik). And the angel is sent to him with instructions concerning four things, so the angel writes down his provision (sustenance), his death, his deeds, and whether he will be wretched or fortunate. Then the soul (ruh) is breathed into him. (Al-Bukhari 1979:63)

According to this *hadith*, each stage of human development is assigned a time period of forty days, which makes for a total of 120 days; however, other *hadiths*

differ and give 40 days as the total of all stages.[2] Additionally, another passage informs us about the stage of ensoulment during the intrauterine life and speaks about "breathing His own spirit" after God forms human beings:

> He who created all things in the best way and He began the creation of man from clay. Then made his progeny from a quintessence of despised liquid. Then He created him in due proportion, and breathed into him of His spirit. And He gave you (the faculties of) hearing and sight and hearts. Little thanks do ye give! (The Qur'an 32:7–9)

Based on these and other similar *Qur'anic* verses and *hadiths*, Muslim jurists determined that until the stages were complete, the foetus had no soul (*ruh*), or that God had not breathed His spirit into the foetus, and therefore, it had not yet been created. In other words, the new creation (the person) exists only after some stage of embryonic development and not at the moment of fertilisation. In the Islamic tradition, ensoulment is assumed as a central value in the discourse about the moral status of a human embryo or even foetus (Saniei 2010). The ensoulment, hence, grants the embryo an exceptional moral status, which is decisively applied for the ethical evaluation of any medical intervention affecting the embryo (Ilkilic and Ertin 2010).

Generally, most of the verses of the *Qur'an* quoted against the destruction of an embryo or a foetus actually deal with life's sanctity. Although the tradition explicitly mentions the beginning of human creation at the zygotic stage, the verses only cover gestation stages from fertilisation to personhood. Indeed, all Muslim jurists agree that the embryonic life is entitled to respect even before ensoulment, becomes progressively more deserving of rights as the developmental proceeds and definitely acquires full rights after ensoulment (Saniei 2012). However, when assessing an issue, religious scholars use the case-based reasoning, drawn on the fundamental principles of *Shari'a*, and also take into consideration similar and related matters. Therefore, before tackling the issue of human embryo research, something must be said on related matters which have already been ruled upon, including Muslim jurists' view on abortion, as well as IVF and the related problem of spare embryos.

4.3 Abortion in the Shi'a and Sunni Schools of Thought

Abortion is forbidden under normal circumstances by nearly all the major world religions. Traditionally, abortion was not deemed permissible by Muslim scholars. All scholars, according to classical jurisprudence and contemporary scholarship,

[2] The following *hadith*, for instance, says: After the zygote (*nutfa*) has been established in the womb for forty or forty five nights, the angel comes and says: 'My Lord, will he be wretched or fortunate?' And both these things would be written. Then the angel says: 'My Lord, would he be male or female?' And both these things are written. And his deeds and actions, his death, his livelihood; these are also recorded. Then this document of destiny is rolled and there is no addition to and subtraction from it. (see Al-Bukhari 1979).

from the four *Sunni* and the *Shi'a* schools of thought, agree that an abortion cannot be performed after the fourth month (120 days) of fertilisation unless it is to save the mother's life. The disagreements are related to the status of the foetus before the fourth month of gestation (Bowen 2003). *Sunni* scholars have held various opinions on the matter, and formed three main positions.

The first, which includes the *Maliki Sunni* and AL-Ghazali from *Shafi'i Sunni*, considers the foetus as sacred as any living human being from the moment of fertilisation. Therefore, any violence to the embryo at any time of pregnancy is considered a crime. The reason for this strictness derives from the concept of the embryo understood as a creature waiting to receive its soul from God. To this end, the seed should never be manipulated once in the uterus in the form of a clot adhering to the wall (Atighetchi 2007). The second, forming the majority view, including the *Shafi'i,* some *Hanbali* and *Hanafi Sunni,* tolerates the practice of abortion only until the foetus has begun to take on the first signs of human form, which, according to a *hadith*, occurs 42 nights after conception.[3] This group considers that the embryo gains its human sacred character when it starts forming human features such as eyes, ears, limbs, flesh, bones, and skin. For them, aborting the foetus before the ensoulment stage is merely regarded unethical, but aborting post-ensoulment is considered illegal and open to tort (Bowen 2003). The third view, including some *Hanbalis* and *Hanafi,* considers the embryo is granted its living-being sacred character after 120 days of fertilisation, as this is the time when the embryo receives the soul (*ruh*) and becomes a human being (Al-Ashqar 1989; Katz 2003).

According to *Shi'a* teaching post-seventh century, conception begins with the implantation of a fertilised ovum, i.e. *nutfah* in the womb, and whatever aborts the implanted ovum is forbidden (*haram*). The contemporary *Shi'a* Ayatollahs (religious authorities) are nearly unanimous in their rulings on abortion before four months of gestation, and this is discussed in detail later. Grand Ayatollah Ali Al-Sistani, who is the highest ranking *Shi'a* religious scholar, stated that abortion is not allowed, except if the continuation of the pregnancy puts a woman's health into an unbearable difficulty (Al-Sistani Official web site 2002). Ayatollah Khomeini, in Iran, noted,

> Termination of pregnancy even at the earliest possible stage under normal circumstances without any reason is not allowed. (Khomeini 1999)

Ayatollah Khamene'i also stated,

> The S*hari'a* does not permit the abortion of a foetus. In the consideration of the honourable *Shari'a*, there is no difference between a foetus less than or greater than four months gestation with regard to this matter. (Khamene'i 1998)

[3] "When forty-two nights have passed over, the sperm drops: Allah sends an angel to it, who shapes it and makes its ears, eyes, skin, flesh, and bones. Then, he says: 'Oh Lord! Is it a male of female?' And your Lord decides what He wishes and the angel records it." (See Ebrahim 1988: 115–116).

Table 4.1 Grounds for abortion in the predominant Muslim countries (Hessini 2007; Hedayat et al. 2006)

Grounds	Countries
Risk to woman's life	All countries
Risk to physical health	Jordan, Kuwait, Morocco, Qatar, Saudi Arabia
Risk to physical and mental health	Algeria
Foetal impairment	Kuwait, Qatar, Saudi Arabia
Genetic disorder	Iran
Rape	Sudan, Egypt
All grounds in the first trimester	Tunisia, Turkey

Ayatollah Fadlallah, a prominent Lebanese *Twelver Shi'a* Muslim cleric, is also opposed to abortion; however, in some circumstances he views it as being permissible. In cases where the woman is in an abnormal amount of danger from the pregnancy, he believes it is permissible to have an abortion (Fadlallah Official web site 2009). This is maintained among all *Shi'a* scholars, although Ayatollah Sane'i considered certain social aspects and ruled,

> Any foetal or maternal condition that brings extreme difficulties *('usr va haraj*) for the mother or the family allows for abortion. (Sane'i 1999)

However, one scholar, Ayatollah Makarim-Shirazi, has allowed it in cases of "extreme difficulty" (Makarim-Shirazi 1998). With regard to the termination of pregnancy, the Islamic scholars all agree that after ensoulment it should only be allowed in cases where the mother's life is in acute danger, otherwise, it is deemed to be homicide (Hedayat 2006).

Recently, scholars have begun to consider the effect of severe foetal deformities on the mother, the families and society. This has led some scholars to reconsider the prohibition on abortion in limited circumstances. Muslim are, however, encouraged to read and analyse traditional religious sources to find solutions to contemporary problems, which differ from country to country. There is no consensus among Muslim scholars on abortion, and every Muslim country has taken up a regulatory policy (see Table 4.1).

4.4 Assisted Reproductive Technologies and the Fate of Spare Embryos

In the 1970s, IVF technique in ARTs to treat human infertility marked the beginning of the revolution in making possible what is naturally impossible. The technique basically involves collecting the eggs, fertilising them in the Petri dish and then implanting embryos into the woman's womb. Thus, sperm and eggs are practically taken out of bodies and then the resultant products are transferred back into bodies. Besides the two to three embryos that are injected for gestation, there are surplus embryos that are frozen for use in further, future attempts. Therefore,

one of the major ethical and social concerns with the IVF technique is about the fate of the frozen embryos; those which are no longer used for their owners' infertility treatment. They are sometimes donated to other infertile couples or for scientific purposes, including stem cell research.

Some Muslim countries prohibit surrogate parenting and the adoption of human embryos on the basis of the importance of kinship, descent and inheritance, which shaped the moral issues of third-party eggs, sperm and embryo donation. Accordingly, third-party donation destroys a child's kinship (*nasab*) and violates the right of inheritance; thus, donating embryos to other couples is forbidden in those countries (Inhorn 2006). Those spare frozen embryos would suffer no legal harm by their destruction as, according to the Islamic law, they could not have developed into a human being (Serour 2005). Hence, this would free the spare embryos for research or discard. It is noteworthy that some Muslim countries, such as Iran, allow research on donated embryos for the advancement of scientific knowledge and the benefit of humanity (Saniei 2012).

In addition, in the case of a multifoetal pregnancy, the procedure requires the abortion of additional embryos to avoid endangering the mother's health and improve the chances of survival for the remaining one (Saniei 2012). In other words, Muslim religious authorities have allowed a form of selective abortion which eliminates one or more foetuses in a high-risk IVF pregnancy with twins or beyond (Inhorn 2011). As mentioned before, Islam is generally permissive when it comes to clinical abortion, since it does not consider life to begin at the moment of conception. It seems that little attention was paid in Islamic juridical deliberations to the moral and social implications of the procedure over the status of multiple human embryos that were produced in the Petri dish and then implanted to increase the possibility of pregnancy (Dickens and Cook 2008).

4.5 Islamic View on Human Embryonic Stem Cell Research

The therapeutic potential of hESCs is one of the most controversially debated areas of embryo research. According to scientists, hESCs are pluripotent and sufficiently able to expand into stable cell lines which are required for both basic and applied research to develop cures against a range of devastating illnesses, such as Alzheimer's and Parkinson's diseases, or to repair spinal cord injuries. The ongoing debate on hESC research largely revolves around the ethical implications of a technique that involves the manipulation of human embryos, i.e. the isolation/derivation of pluripotent hESC lines from spare embryos created for the purposes of ART (Baharvand 2009). The most common argument against hESC research is that this field of science involves the destruction of human life, as its opponents hold that life begins at the moment of conception. These people often support the IVF technique, despite the fact that IVF clinics routinely discard spare embryos which are the main source of hESC lines. However, there are many opponents of using embryos for research who are also opposed to IVF or to the creation of surplus embryos.

Indeed, scientific advances and the increasing availability of the IVF technique have resulted in an increasing number of frozen embryos which are excess to the needs of couples in cases of successful treatment. If couples have no further desire to reproduce, they are faced with difficult choices about their frozen embryos, including discarding or donating them either for infertility treatment or for research (Dickens and Cook 2008). As mentioned earlier, Islamic law prohibits the adoption of human embryos due to the importance of determining a child's true parentage and inheritance right (Inhorn 2006). Accordingly, donating embryos to other couples is out of question in Islamic tradition. In addition, there would be cases in which couples cannot use their own frozen embryos for religious reasons: In the *Shari'a*, for instance, because any form of IVF implying procreation outside of the framework of an existing legal marriage would be forbidden. Therefore, the embryo could not be implanted after divorce or if the donor of the oocyte or the sperm had died (Serour 2005). Therefore, it seems that this leaves the door open for research (Weckerly 2002) or discard.

Hence, the moral significance of the embryo at its early stage of development remains at the centre of the controversy associated with the permission to use it, while its destruction for harvesting stem cells (SCs) is incompatible with the notion of embryonic sanctity and the respect for the pre-implantation embryo (Sachedina 2006). In fact, there is no exact definition of an embryo as a living entity right from the zygotic stage anywhere in the tradition. The Muslim jurists have mostly regarded implantation of the zygote in the uterus as the determining stage of foetal life when any infliction of harm to it requires compensation. This ruling is extrapolated from the interpretation of the following verse in the *Qur'an* that reads:

> It is He who produced you from one living soul (*nafs wahida*), and then a lodging-place (*mustaqarr*) and then a repository (*mustawda'*)." (The Qur'an 6:98)

"A lodging place" is the uterus, whereas "a repository" is the loins in which specific characteristics are preserved for future generations. Obviously these rulings in no way suggest an endeavour to define the beginning of foetal life in the womb (Ibn Kathir 1966). In the context of IVF technology, some scholars hold the distinction between the "implanted" embryo which is developing in the uterus and the "spare" embryo that exists outside of the woman's body and has never reached the stage of ensoulment. As discussed earlier, the moral significance of the foetus in Islam has been connected with its development to a particular point when it gradually attains human personhood with full moral rights. Based on the *Qur'anic* passages, the implanted zygote is considered as a rights bearer. Consequently, many Muslim jurists do not treat the embryo outside of the uterus as a rights bearer (Sachedina 2009). However, many Muslim scholars have approved the creation of hESC lines for research and therapeutic use, even if it involves the destruction of surplus IVF embryos, in that very few of them will have the chance to develop into mature human beings. The more plausible view among Muslim jurists is that human entities at the beginning of life do not have a moral status, and hence, the use of them for research purposes is justifiable.

Some argue that while these are justifiable objections, the spare IVF embryos will, in any case, be destroyed; therefore, there is no reason why they should not be used for the general good (*maslaha*), such as approving their use for embryo research which gives the hope of providing the cures for debilitating conditions. Moreover, because this research could lead to cures for diseases that are now fatal, it might even be obligatory. Accordingly, the embryo's destruction during the process of the derivation of SCs cannot be ethically acceptable. However, there is also an absolute moral obligation (*fard kifayah*) in Islam for the physicians and scientists to undertake biomedical research that may result in beneficial treatments for so far incurable diseases (Siddiqi 2002). Nonetheless, there is an equally valid concern whether the potential benefits of hESC research can certainly be translatable into therapy. This requires Muslim scholars to provide the evidence related to the standards of the ethical and scientific oversight. They thus need to assess the potential risks and benefits of hESC research in the light of Islamic values and embryonic sanctity. Therefore, as stated by Abdulaziz Sachedina:

> It is correct to suggest that a majority of the *Sunni* and *Shi'a* jurists will have little problem in endorsing ethically regulated research on the SCs that promises potential therapeutic value. (Sachedina 2000)

4.6 Human Embryonic Stem Cell Science: The Case of Iran

Iran is one of the countries in the Middle East that has quickly established a field in hESC research. The country's supreme religious leader, Ayatollah Ali Khamenei, issued a *fatwa* in 2002 establishing that hESC research was permissible within *Shi'a* Islam and encouraged scientists to pursue this research with the purpose of advancing science and technology to save lives (Saniei and De Vries 2008). This positive decree could ultimately be credited for active research programmes in the field of hESC science. The Royan Institute has since become one of the leading SC research centres in the Middle East region, creating a hESC line in 2003 (Baharvand et al. 2004). Other research institutes have been actively involved in regenerative medicine. These include the Iranian Molecular Medicine Network (with 34 members), the Iran Polymer and Petrochemical Institute and Shaheed Beheshti University of Medical Sciences (Kinkead 2003). In March 2003, the Islamic Republic News Agency (IRNA), the official Iranian press agency, announced that the country was among the first ten countries in the world that were capable of producing, cultivating and freezing hESCs. Thus, Iran is in the group of countries, such as Sweden, the UK, Japan, South Korea, and Singapore, that can produce hESCs, and it is the only Muslim state to do so (Saniei and De Vries 2008). Moreover, the birth of Royana, the first cloned lamb in Iran, in 2006, and of Hanna, the first cloned goat in the Middle East and the fifth in the world, in 2009, prove that Iran has progressed remarkably in science, and special attention should be paid to this country in medical issues and ethical debates as well

(Royan Institute 2009). In 2008, Royan Institute scientists claimed that they had also succeeded in reprogramming human skin cells to an embryonic-like state to create so-called induced pluripotent stem (iPS) cells[4] (Iran Daily 2008).

Currently, there is no parliamentary legislation directly related to hESC science. Rather, the need to control human embryo research led the Iranian government to put forward "Ethical Guidelines for Gamete and Embryo Research" in 2005, regulating and determining certain circumstances for the use of human embryos in research and therapy (Saniei and De Vries 2008). According to the guidelines, the use of human embryos should be based on voluntary and informed participation in research and respect for human dignity and human rights, as well as for privacy and confidentiality. The guidelines mention that the benefits and harm caused by research on the embryo should be carefully taken into consideration. The guidelines allow the use of surplus IVF embryos for research purposes if the embryos are not older than 14 days, but do not allow the generation of human embryos with the sole purpose of doing research. Moreover, the guidelines prohibit the production of hybrids by using human and animal germ cells, and also eugenics applications. Responsibility for the embryo is left to the donor, her partner and the recipients, who are permitted to obtain any information regarding research.

It is noteworthy that the rules, regulations and practice in Iran are based mainly on *fatwa*, which are not the result of public and secular debate (Aramesh and Dabbagh 2007). Iran has a centralised *Shi'a* authority, represented by the Grand Ayatollah, who occupies the highest religious and legislative power in the country. The importance of this fact is that the assessment and practice of any subject are based on religion, which more readily provides clear and direct information about the country's approaches to embryo research, at least from a *Shi'a* perspective. Moreover, this religious constitution facilitates and speeds up the decision-making process. It can even open the way for research when there is no legal regulation on a certain subject.

4.7 Conclusion

The ethical and religious assessment of the use of human embryos for research in Islam can be inferentially deduced from the rulings of the *Shari'a* that deal with foetal viability and embryonic sanctity in the classical and modern juristic

[4] Induced Pluripotent Stem Cells (iPSCs) are similar to natural pluripotent stem cells, such as embryonic stem cells, in many respects, such as the expression of certain stem cell genes and proteins, chromatin methylation patterns, doubling time, embryoid vody formation, viable chimera foundation, and potency and differentiability, but the full extent of their relation to natural pluripotent stem cells is still being assessed. iPSCs were first produced in 2006 from mouse cells and in 2007, from human cells. This has been cited as an important advance in stem cell research as it may allow researchers to obtain pluripotent SCs, which are important in research and potentially have therapeutic uses, without the controversial use of embryos. Because iPSCs are developed from a patient's own somatic cells, it was believed that treatment with iPSCs would avoid any immunogenic responses; however, this assumption is still challenged (see Takahashi and Yamanaka 2006).

decisions. As technological advances and scientific inventions continue to provide new challenges, Muslim jurists have used other available methods in principles of Islamic jurisprudence in order to find Islamically valid solutions. In general, Islam is thought of as being tolerant of human embryo research. Indeed, a positive view of embryo research prevails among Islamic religious scholars and in the national and international Islamic law councils. While legal opinion (*fatwa*), according to Islamic religious law, i.e. *Shari'a*, permits human embryo research, this does not, however, mean that there are no restrictions. Embryo research and stem cell science are regulated by law in different ways in the countries in the Middle East. Many countries have some form of regulation, for instance, for ARTs, but hardly any of them have regulations for human embryo research and technology, even in a well-established country such as Iran. Hence, as stated by Sachedina (2009), for those Muslim jurists who wanted to provide moral-legal justification for the use of "spare" embryos as the source for research, e.g. hESC research, juridical solutions were not hard to deduce when legal principles, such as public good *(maslahah)*, that promotes what is beneficial, and necessity (*darura*), that overrules prohibition, could provide religious-legal justification and legitimization.

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Chapter 5
From Farming to Pharming: Transcending of Bodily Existence as a Question of Medical Ethics in an Intercultural Context

Axel Siegemund

5.1 Pharming: Prostitution of Nature?

"Theology of Land", written by Bernard F. Evans and Gregory D. Cusack, was published by the Liturgical Press in 1987. It stated that farming has morphed from its ethical and spiritual roots to become chemical pharming.[1] But what does this mean? Natural food has ethical roots, but are chemical products unethical objects? Traditional farming is just another way of spiritual life, but is chemical pharming an action against this life? Is biopharming going to overreach the fundamentals of our existence? Has farming already been a natural way of agriculture, while chemical pharming is a prostitution of nature?

I want to show some ethical challenges of chemical pharming. The leading question is, whether it is really as far away from traditional farming as some people think it is? How do the questions on pharming differ from those on farming and which ethical concerns remain the same?[2]

Farming means to use creations such as cows, crops, pigs, and trees to produce food and to form a cultural landscape; but it is also a way to produce artificial creations. Farm animals, such as cows and chickens, are part of the productive livestock; they have been products of culture for centuries: Technologies and created nature come together. Nowadays, in a genetically modified plant, actually the same process takes place: Genetic engineering is based on natural and cultural roots we cannot avoid.

[1] I will use "biopharming" and "chemical pharming" synonymously.
[2] Compare this to the general aspects of Nunziata Comoretto's Chap. 6 in this volume.

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Pharming is a challenging application of biotechnology, linking questions of environmental ethics, animal welfare and medical ethics. It means to produce pharmaceutical products using genetically modified plants and animals as biological and quasi-biological factories. Recent studies see pharming as a potentially competitive way of producing biopharmaceuticals (Engelhard et al. 2008). In some cases, it may be the only way of producing particular proteins; in other cases it may be the cheapest one.

So farming and pharming are based on the creativity of created humans (cp. Hefner 2003). That is why in the case of chemical pharming, the principal goodness of creation (Rendtorff 1988) and the possibility of failing the good (Graf 1990) will overlap. Pharming is a way to use or misuse our freedom, which is a significant attribute of man. However, there is no difference between farming and pharming concerning this aspect. However, the historical roots of our technological society show that the consequences of the goodness of creation, as well as the consequences of the evil, are materialized in the structures of life, as well as in the structures of technology. We know that traditional farming was directly connected to slavery, so even prostitution of nature is not a modern way of chemical life only. The ethical challenges of biopharming are not a consequence of the fact that this is a special technology. They are rather a consequence of the fact that it is a human activity—an activity of the free man.

As there is no option for us to relinquish cultural deforming of nature, we have to find a way to bridge the lack of natural conditions and our technological knowledge. The ethical question hereby is if we will succeed or fail to build this bridge. Prostitution of nature would indeed mean to fail in our task due to the disintegration of natural conditions and cultural context. The challenges of pharming in different cultural contexts follow the technological and environmental concerns of farming (see Sect. 5.2), because covering nature is not a new task for the twenty-first century only. However, the technological options today are closer to the anthropological aspects of the human condition than in traditional societies (see Sect. 5.3). That is why a risk-benefit evaluation may be not enough to make pharming an acceptable technology in different cultural contexts.

The main question is, how our creative skills will influence our concepts of covering nature by forming a technologically driven society. Farming and pharming are creative activities of humans, but the products of these technologies are not the ultimate scope of life. They are (only) a need for this life.

5.2 Technological and Environmental Concern

The use and misuse of the freedom of creation differs from culture to culture since they are not fixed by legal and illegal actions. Hereby, “freedom of creation” describes the fact that life is a given life—no one can produce himself. While European society will look at ecological aspects very carefully, others, such as Asians or Southern Americans, will concentrate on the way of implementing

animal-like products. A vegetarian society, such as the Indian one, will not distinguish between products from natural animals and those from genetically modified animals—flesh is flesh—and using the carnal nature for our own purpose means to misuse it. So medical ethics has to be engaged in the intercultural concepts of the self-image of man, of nature and of technology when establishing this new branch of biotechnology. The technological and environmental programs of global societies, as well as the different ways of connecting and disconnecting nature and technology, have to be observed. These programs, not chemical pharming itself, are the place of the use and the misuse of our freedom.

Pharming means not only to produce medicine, but also food. We should not keep people away from the possibilities of these technological efforts. People especially of low-income countries could benefit from this. We should consider how to use the natural and the historical roots we are living from. Therefore, we have to look at the very different meanings of nature, environment and technology.

The economic philosophy, for example, has shaped North American attitudes towards property in general. Models for responsible landownership based on the Euro-American ethical heritage will be very different from Asian models. The dominant Euro-American tradition is the tradition of owning land. If pharming is a way of making land become a factory, then owning land means owning the basic requirement of this technology. Estate owners become owners of the technology. So the aspect of production is to reflect on alternative systems of environmental ethics. The land-use ethics of contemporary western society is an economic ethic: The value of land is determined almost exclusively by its role in the market system. Thus, pharming will bolster up this role.

One challenge of environmental ethics is to consider the way of handling animals, plants and land as "factories", far away from their use as food (Rosenberger 2007). John Lock says, land has no real value until it is "improved", that means when labour is added to it (Cohen 1995). The focus here is what one can claim for oneself. However, when we think about pharming as a way to produce medicine, we have to think about our social obligations. We will need a human rights starting-point that acknowledges social and economic rights as well as social and economic responsibilities. What should be expected of a technology is that it is beneficial to single *as well as* global societies. Thus, pharming should make use of the evolving concept of social responsibility within a framework of human rights and responsibilities. Pharming is a technology which needs natural resources, but it also needs know-how, education and professional skills. Can such a naturally- and genetically-based technology allow us to displace individual rights by the common good?

The idea of a common good, as well as the idea of environmental protection, presume perpetuity; they presume an open future: Here for a single society, there for the global community. So the protection of the environment is only reasonable when the structures of our thought exceed our own life: Environmental concern is a multi generational task and it is a link between different societies. This does not, however, mean that the environment has to become a personal subject. "Nature" especially is not a subject for itself.

At this point, we have to connect our ethical knowledge carefully to the anthropological aspects[3], especially the creation-focused spirituality of different peoples. They are multicultural sources for rethinking the environmental concern: "Creation" is the description of a value-linked nature, while the objects of natural sciences cannot include values and goals. But technology is neither spiritual nor scientific. "Technology" means bridging physical laws and cultural aspects. This is why every single technology is formed by "laws of nature" plus "anthropological conditions".

Therefore, when biopharming goes beyond present borders, we need to assure the protection of the fundamentals of this "going beyond". We not only have to shelter animals and plants, but also to acknowledge the historical, ethical and religious background of the land's habitants. Finally, these factors will mainly influence whether such a new technology is a reasonable and helpful contribution to current problems in food and medicine supply, or rather a destruction of resources and painful invasion for people and nature.

5.3 Pharming: Transcending of Nature

Actually, there are three ways in which people try to transcend their lives: History, religion and technology (Heyd 1992). History means to break down the barriers of lifetime. One's life becomes part of universal history. Religion means to attain the highest good, which is impossible in the solitary lifetime of a human being itself. The third way is bearing down the barriers of our bodily existence by practice. So Arnold Gehlen described technology as the compensation of organs (Gehlen 1957). John Rawls called the ethical aspects of transcending one's life (1) the everlasting moral agent and (2) the collective enterprise of the promotion of justice (Rawls 1999).

The philosophical anthropology of Western Europe especially is a philosophy far from bodily existence. That is why the technological access to the human body here is much easier than in other cultures. Helmuth Plessner, a German philosopher and anthropologist of the 20th century, says that environmentally interactive organisms realise their lives in the act of self-positioning (Plessner 1928). The self-expression of plants is to be utterly open; they cannot express any preferences. Contrary to plants, animals are aware of their borders. They are centric organisms. Human beings alternate between the openness of the plants and the closed intentionality of animals. Humans have borders and they represent these borders. So humans are eccentric in environmental relations. Only human beings can transcend their bodily existence by practical thought.

Immanuel Kant said that practical thought is supported by freedom, perpetuity and the existence of God (Kant 1977). The theological impact of these postulates

[3] The term "anthropology" will be used to describe the philosophical and theological knowledge about man—in contrast to the Anglo-American use of "anthropology" as a biological term.

are the freedom of creation, the perpetuity of the processes of life and the guaranteed future for human life.

So the ethical challenges of biopharming follow the anthropological question: What does bodily existence mean? "Technologically", biopharming means that plants and animals are used to transcend our nature by the production of food, medicine and enhancement through the practice of genetic engineering and synthetic biology. "Environmentally", pharming means making agricultural land become a factory for the production of non-food articles. "Anthropologically", it is a technology which follows very different historical and religious ways of transcending our lives in an intercultural context.

5.3.1 The Dignity of Freedom

Transferring a technology from one cultural context to another means to create a new technology. Due to the fact that the embedded factors of a specific technology are considerable for its success, one cannot desist from political, economical, religious, and scientific aspects. Especially, we cannot desist from the global discourse about the dignity of life. Pharmaceuticals are produced to be brought in contact with the human body. How does the cultural impact influence the acceptance of products developed by pharming (Pardo et al. 2009)?

To answer this question, the relationship between research and cultural impact has to be considered in both directions. Our western understanding of the freedom of research influences the products of pharming, as well as our understanding of dignity. The meaning of animal rights influences the way of research and its benefits; and vice versa, the production of biopharmaceuticals and the possibility of their utilization influence ethical standards. Thus, the ethics for genetic engineering will be different from the ethics for landscape farming.

The moral aspects do not change just because of changing ethical concepts, but because of a different anthropological impact. The relationship between people, nature and technology becomes closer due to the technologically-driven change of the environment. So we have to accept that relationships differ from culture to culture. However, not all relationships are equal and not all relationships have an equal right. What does this mean for the ethical standards in a global context? We do not have to think that our own standards would be the best elaborated findings and convictions. But we also do not have to disclaim our well thought-out standards. We are not free to do with our technologies as we please. We have to bring the ethical standards into the discussion as thoughts of a special culture. This special culture is not bordered by ethnic, religious or political frontiers. It is defined by a common basis. I suggest that freedom could become a common basis as it is a pre-condition of rethinking ethics.[4]

[4] Compare to the presentation of Nunziata Comoretto's Chap. 6 in this volume.

One culturally developed basis of ethics is the dignity of free people. However, the dignity of man, which we find in political discourse, differs from the dignity of man as God's creation, which is suggested by theological ethics. We, created in God's image, have rather been endowed with the responsibility for maintaining justice and righteousness within the dominion; but "created in God's image" is an ethical basis of a special theological context.

The cultural impact of bodily existence, which influences the acceptance of products developed by the use of genetically modified plants and animals, will differ from Christian to Hindu thought, and these will differ from Islamic thought. This situation requires the restoration and preservation of all the resources of this domain. This requirement follows the dignity of free creations in a very practical way: People of low-income countries recognise the collision course of our technosphere in a different way than we do. These people are faced by the environmental problems day by day. The ecological crisis, produced by our western technology, matters to their bodily existence directly. It matters to their dignity and it limits their freedom. What will displaced people expect from another new technology? These people know that the way of industrialisation was a human-centred way of western society—so they will speak about the need to shift from human-centredness to maintain the dignity of man, as well as the dignity of natural life.

5.3.2 The Perpetuity of Creation

Plants and animals are traditionally seen as special parts of the creation. Genesis 1 in the Old Testament informs us that the creations reflect the glory and beauty of God, their creator. However, genetically modified plants and genetically produced animals are creations of our own technological thought and handling. Here we have to think carefully about the religious meaning of pharming as a technology of man: Do the products of biopharming reflect the glory and beauty of their creator, the technologically handling man?

In Genesis 1, Adam (which means "mankind") has a partner, Adamah (which means "land"). "Man" is taken from "land". Humankind and land are linked in a convenient relationship, analogous to the convenient relationship between man and woman. Walter Brueggemann, an American Protestant Old Testament scholar, says that we shall not have a new environmental ethic until we have a new social ethic, free from promiscuity and domination. Applied to nature, it means we shall not have fertility until we have justice towards nature and towards those who depend on it (Brueggeman 1987).

The biblical creation-focused ecology involves the rescue of both humanity and environment from oppression. The Sabbath in biblical tradition is more than a day of compulsory worship (Zenger 1988). Through the Sabbath tradition, the Hebrews discovered man created design in relations between God and the world, between humanity and nature, and within human society. One important relationship of our

society is that between technology and nature. The authors of Genesis understood the cycle of this relationship: Work was not complete until there was rest, reflection, worship, and celebration. The perpetuity and the principal goodness of creation are pre-conditions of our environmental concern for this creation.

In the western world, for the first time in history, the majority of men and women do not even work in direct contact with agriculture and land. If biopharming is a way to leave the earth to machines and to train a few people to think like machines, it will indeed become a misuse of our freedom. But this is only one option for our future; another is rethinking the promise of and for a created world.

5.3.3 A Technologically Driven Change of Mind

Our question is: Can the production of food and medicine by genetically modified plants and animals be used to rebuild relationships between people, nature and technology? I will give two pieces of advice concerning what we have to consider:

1. Not only a handful of individuals and corporate controllers should benefit from biopharming. Those made wealthy from nature and technological knowledge should not form an elite expecting to profit from the poverty of the masses of displaced people. That is why even traditional agriculture has already changed the situation of people. We can use the ethical experiences of traditional farming while facing chemical pharming. Tribal people, for example, were traditionally dependent on agriculture to sustain themselves. A technology-driven change of mind and life managed by NGOs is already helping these people to help themselves.[5]
2. The acceptance of genetically modified products will depend on the different embedded factors of history and of religion. Thus, genetic engineering in Germany is facing the problem that consumers are not ready to accept gene-food. In other countries, gene-food is not an ethical problem of the consumer side; it is a problem of the production side. Suicides of farmers in India and Latin America show the tremendous effects of genetic engineering, as well as the long-term protests in Germany. These effects, however, are not effects of the technology, they are effects of their embedded factors.

[5] Compare to widango.net. In January 2001, traditional crops constituted paddy, ragi, maize, and niger. With the advent of the NGO WIDA (Weaker Integrated Development Agency) in Orissa's Koraput District, India, the tribal people have been taught to cultivate more economic crops, such as potatoes, beans, cabbage, cauliflowers, ginger, and chillies. One model village is Porjapungar. Before the NGO came to this village, the villagers barely managed to coax out two or three crops, such as maize and onions, from the soil. Now, the villagers have a better idea about cultivation. This development intervention follows the way of "traditional" farming and it has helped in more ways than just in cultivation or increasing income levels through it.

In summary, biopharming should not only be seen as producing food or medicine. At the same time, it could become our chance to restore the relationships between humans, nature and technology. Therefore, we need to think beyond short-term benefits and bethink ourselves of justice and peace, especially for those who do not have access to modern life. Clearly, this would mainly increase the acceptance of such a new technology and enable trustworthiness in it.

5.4 Conclusion

Biopharming, as a very new technology, allows us to go beyond the limits which were established in the previous courses of history and religion (Schockenhoff 1998). It is a relatively new task to evaluate technology as one way of transcending our existence. Future questions of research ethics will connect the historical, the religious and the technological aspects. The transfer especially of the technological paradigm into non-European contexts is a question of the ethics of technology. While in the last few decades the discussion was focused on the relationship between the development of natural sciences and the Judeo-Christian tradition (causality and the time-bar model), future debates will be about the integration of technological concepts into Muslim or Hindu contexts.

A creation-focused spirituality especially follows a strong link of Monotheist religions. Any concept of human domination over the rest of the world is very foreign to biblical ecology, as well as to Christian thought, but most Arabic or Indian concepts of ethics are indifferent concerning the technological development. A very new technology, such as chemical pharming, can become an advantage for social change, for educational efforts and coalitions with groups able to work together on specific issues: It will be more necessary to think about ethical and religious links between technology and society.

> Often the arguments for and against biotechnology remain relatively abstract and tend to be defined by the trade-off between the type of goals pursued, biomedical in our case, and the methods applied—genetic modification of plants or animals. Yet, from an analytical standpoint, and for the purpose of communication with the public, it is interesting to gauge the sensitivity or elasticity of people's attitudes in response to the presence of more specific goals and means. (Pardo et al. 2009).

What is gauging "the sensitivity or elasticity of people's attitudes"? It is exactly the reflection on the roots we come from and the imagination of our future. Reflecting this means to use history and religion as sources for an open future. The task is to rebuild human relationships while rebuilding the self-image of man through a technology-driven change of mind which follows the historical and religious ways of transcending the lives of free people. The temptation will be to replace the traditional transcendences by technology. One instrument of rebuilding relationships is to educate people how to use biotechnologies in a better way. The efforts of development policy show that a technology-driven change of mind and

life is possible. Research ethics means to manage bridging science, technology and society; it does not mean to forbid or to allow a specific way of development.

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Chapter 1
Introduction

Jan Schildmann, Verena Sandow, Oliver Rauprich and Jochen Vollmann

1.1 Human Medical Research: A Brief Introduction

Ethical and empirical questions of human medical research have been analysed from the perspectives of a broad spectrum of scientific disciplines. At the same time, the issue is a topic of public and political debates. Besides frequently discussed topics, such as informed consent or the appropriate assessment of risks and benefits in clinical research, new questions, such as ethical and empirical aspects in the context of "personalised medicine" and ethical issues of global medical research, have caught the interest of scholars from normative and empirical disciplines. Moreover, the development of natural and medical sciences poses new challenges to established concepts, for example, the doctrine of informed consent in the context of non-interventional human genome research.

Looking at current scientific activities on the topic of ethical, legal and socio-cultural aspects of human medical research, it is one characteristic that the related investigations make use of methods and approaches from more than one discipline. This is illustrated by the fact that many researchers in the field have qualifications in more than one speciality. A second feature which may be cited as characteristic for the current investigations is the emphasis on contextual aspects, such as the historical and socio-cultural environment in which human medical research takes place.

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This volume provides an overview of the work of young scholars on the ethical, legal and socio-cultural aspects of human medical research who share an interest in multidisciplinary and context-sensitive approaches to this topic. All papers are the result of the project "Human Medical Research—Ethical, Economical and Socio-Cultural Aspects", which was funded by the German Federal Ministry of Education and Research in 2010–2011 (FK 01GP1086). Following the call for abstracts, 14 researchers from nine countries have been selected to present their work as part of the conference "Human Medical Research—Ethical, Economical and Socio-Cultural Aspects", which took place from 7–11 February 2011 at the Institute for Medical Ethics and History of Medicine, Ruhr University Bochum (Germany). One focus of the thorough discussions during the conference, as well as the following peer review process of these papers, was to analyse each project from the viewpoint of the different disciplines represented by the authors. In addition, it was also asked to what extent each project may be relevant to other pieces of work presented during the conference and as part of this book. Based on the selected contributions, as well as on the focus which emerged as part of the discussions throughout the joint work, the book contains four parts which will be presented briefly in the following.

1.2 Historical and Socio-Cultural Contexts in Medical Research

The first part of the volume introduces historical and socio-cultural contexts of medical research and provides an insight into the diversity of approaches within the field.

The first chapter in this section, by *Fiona McClenaghan*, deals with the British response to Nazi medical war crimes in Chap. 2. It illuminates the expectations that the British had of German research activities and their dilemma when they had to face the fact that Nazi science had used human subjects for inhumane experimentation. The question of whether or not to use the results of German science that were brought about by wrongful means was one problem the British government was faced with. Those conflicts could not be easily resolved.

From his clinical experience in psychiatry, *Rael D. Strous* illuminates the challenges in medical education with regards to medical research in Chap. 3. The author argues in favour of the use of history in the teaching of research ethics and provides examples of possibilities to develop ethical decision-making competency with regard to ethical questions in human medical research.

In Chap. 4, *Mansooreh Saniei* contributes to the topic of research with human embryonic stem cells and on the use of human embryos for research purposes from an Islamic perspective. Based on an empirical study conducted in Iran, she provides an insight into a number of issues related to the regulation of research with human embryos in a country with a strong religious background.

Axel Siegemund, in Chap. 5, explores ethical and anthropological aspects of the use of modern bio-techniques for agricultural purposes from a theological

perspective. The author focuses on the genetic modification of organisms, contrasting this "pharming" with traditional farming. The use or misuse of the freedom and creativity of man is an old problem but poses new challenges when facing the extensive changes in landscape, life and society brought about by technology.

1.3 Considerations on Ethical and Legal Regulations for Medical Research

The second part of the book addresses ethical and legal regulations relevant to human medical research.

Chapter 6, by *Nunziata Comoretto*, starts with the fundamental distinction between clinical research and clinical care. Physician-investigators have a therapeutic obligation to each research participant, not simply an obligation not to exploit participants for the sake of scientific investigation. Besides the therapeutic obligation paradigm, the non-exploitation paradigm is one of the central aspects in clinical research. Referring to the Declaration of Helsinki (and all its ethically relevant changes in the past few years), the author illuminates an ethical guideline to concretise these physicians' obligations and paradigms.

The international human rights law and different standards for research participant protection are the objects of Chap. 7 by *Ilja R. Pavone*. The issue of so-called double standards for "developed" and "developing" countries has become part of most regulatory frameworks in biomedical research. In this respect, the author reviews and compares existing ethical guidelines, such as the Declaration of Helsinki, with the rules for research practice in developing countries.

In Chap. 8, by *Tomasz Zimny*, the focus lies on the European patent law, with its crucial rules and ethical challenges in the context of human medical research. The author describes the aspects of morality, which have gained importance in patent law and which can be analysed with regard to various aspects.

Chapter 9, by *Susy Olave Quispe, Duilio Fuentes Delgado, Gabriela Minaya Martínez* et al., offers an insight into practical experiences related to the development and validation of a guideline for Peruvian research ethics committees. Ethical and scientific aspects of clinical trials are taken into consideration in order to formulate institutional standards.

1.4 Conflicts in Medical Research

The third part of the volume deals with normative conflicts in medical research.

Chapter 10, by *Verena Sandow, Jan Schildmann and Jochen Vollmann*, clarifies the different concepts of conflict of interest and conflict of obligation, and analyses the underlying ethical principles. In addition, concrete suggestions for the management of conflict of interest in human medical research are made.

Annelien L. Bredenoord and Johannes J. M. van Delden, in Chap. 11, concentrate on the question of how to deal with individual genetic data, which are identified as part of genomic research projects. The authors propose different ways regarding the feedback of data to the participants based on the balance of relevant interests and ethical principles.

Chapter 12, by *Anna E. Westra, Jan M. Wit, Rám N. Sukhai* et al., focuses on human research with children. In the case of the so-called "higher risk no direct benefit studies", children cannot directly benefit from their participation in the study. In their analysis of the different ethico-legal frameworks in Europe and the USA, the authors present and discuss the relevant ethical principles at stake.

1.5 New Developments in Medical Research and Ethical Implications

The volume's last part focuses on ethical challenges posed by recent scientific developments.

In Chap. 13, *Rieke van der Graaf and Johannes J. M. van Delden* reflect on the possible duties we owe to human beings in the context of humane medical research. Whereas the debate in the past focused very much on negative obligations towards human research subjects, such as the non-exploitation paradigm, the authors argue for a paradigm change of research ethics which also includes positive obligations owed to research participants.

Chapter 14, by *Flavio D'Abramo and Cecilia Guastadisegni*, deals with the ethical and epistemological issues of using cancer molecular biomarkers in the context of so-called "personalised medicine". In their contribution, they focus on the ethical aspects of fair allocation of resources in light of the high cost for the development of individualised cancer treatment, as well as the ethical implications of genetic-based "personalised medicine" for the physician-patient relationship.

The last chapter in this volume, Chap. 15 by *Kristi Lõuk*, points out ethical considerations on the distinction between interventional and non-interventional types of human biomedical research. She argues that reference to biobank exceptionalism for non-interventional research has failed to provide a helpful basis for ethico-legal regulation. In her account, the author proposes focusing on the role of the investigator and the actions involved in specific biobank research projects as a criterion to judge such projects from a normative perspective.

This book is addressed to researchers from different disciplines working on the normative and empirical aspects of human medical research. In addition, we consider the combination of conceptual and empirical work in this book as relevant for those who deal with the practice and regulation of human medical research. We are very thankful to all the authors for their articles and their willingness to contribute to this volume. We also thank the German Federal Ministry of Education and Research for funding this project (FK 01GP1086).

Part II
Considerations on Ethical and Legal Regulations for Medical Research

Chapter 6
Rethinking the Therapeutic Obligation in Clinical Research

Nunziata Comoretto

6.1 Introduction

Since randomized controlled trials (RCTs) became the leading method of testing treatment efficacy, a plethora of concerns have arisen about the ethics of human medical research. Highly debated issues are the use of placebo controls when proven effective or standard treatment exists (Rothman and Michels 1994), and—strictly connected with this topic—the ethical distinction between clinical research and clinical care (Brody et al. 2003), as well as methodological considerations pertaining to the scientific validity of clinical trials (Freedman et al. 1996a), appropriate ethical standards of risk-benefit assessment for clinical research (Wendler 1998), and a sound public policy for drug development (Sollitto et al. 2003). Before addressing each of these major topics, a clarification about the objectives and principles that outline the ethical status of human medical research is required.

In this regard, two main ethical approaches have been distinguished: The "therapeutic obligation" paradigm and the "non-exploitation" paradigm. After an overview of these approaches, I will analyse the ethics of the Declaration of Helsinki, a cornerstone of research ethics, in order to show possible connections with the ethical paradigms mentioned.

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6.2 The Therapeutic Obligation Paradigm

The therapeutic obligation poses an argument: As the principle of therapeutic beneficence is central to the entire body of medical ethics, physicians should always promote the medical best interest of patients by offering optimal medical care. It follows that the risks of prescribed treatments are justified only by the potential therapeutic benefits to patients.

On this basis, Freedman (1987) formulated the principle of "clinical equipoise", which has become a widely accepted principle governing the ethics of RCTs. As a normative matter, this principle prohibits "any compromise of a patient's right to medical treatment by enrolling in a study". To achieve this goal, the principle requires, on one hand, a genuine medical uncertainty concerning the relative merits of the various treatment arms included in the trial's design; on the other hand, it allows for testing new agents only when sufficient information has been accumulated to create a state of clinical equipoise.

Of course, the therapeutic beneficence governs clinical trials, but not the whole of human medical research. In fact, physician-investigators can ethically perform research procedures that pose a certain degree of risk, but not compensated by any therapeutic benefits to volunteers (Appelbaum et al. 2009).[1]

An ethical framework for the evaluation of the risks and benefits of human medical research should, therefore, draw on a fundamental distinction between therapeutic and non-therapeutic procedures (Weijer 2002). The major intent or purpose of administering a treatment in clinical trials is to offer a chance of therapeutic benefit, and secondly, to test hypotheses concerning safety and efficacy of that same treatment. There should never be a lack of personalized attention to patients in clinical trials, even if these provide treatment according to a scientific protocol. The use of placebo-controlled trials (PCTs) in the face of proven effective treatments, for example, violates the physician's therapeutic obligation to offer competent medical care to patients.

Therefore, therapeutic beneficence requires that procedures administered with therapeutic intent must pass the test of clinical equipoise. Procedures not administered with therapeutic intent are subject to an ethical requirement of minimizing risks and are justified by their potential to generate scientific knowledge.

6.3 The Non-Exploitation Paradigm

The critique of the argument of therapeutic obligation, instead, clearly distinguishes physicians in clinical practices (who have a duty to offer optimal medical care) from physician-investigators in clinical trials (who are not offering personalized medical therapy for individual patients; rather, they seek to answer

[1] On this specific topic, see Kristi Lõuk's Chap. 15 in this volume.

clinically relevant scientific questions by conducting experiments in groups of patients). According to this latter perspective, the process of treatment in clinical trials differs radically from routine clinical practice methodologically: The features of research design, such as randomization, placebo, restriction in use of concomitant medications, etc., are aimed at promoting scientific validity, not therapeutic benefit. It also differs ethically: The obligations of physicians-investigators are not the same as the obligations of physicians in routine clinical practice; investigators simply have a duty to avoid exploiting research participants, not a therapeutic duty to provide optimal medical care. Accordingly, enrolling volunteer patients in PCTs that withhold proven effective treatment is not fundamentally unethical as long as patients are not being exploited.

According to Miller (2002), the major author of this argument, non-exploitation means that patients are not being exposed to excessive risks for the sake of scientific investigation. Risks of concern include death, irreversible damage, temporary disability, and short-lived but severe discomfort. However, in this paradigm, there is no reasonable way to exactly formulate the probability, severity and duration of potential harm that would make the risks of placebo controls excessive. It calls for judgment made by research sponsors, investigators and, most importantly, by IRBs and research participants (once approved by IRBs, patients make their own judgments about whether they are prepared to accept the risks of trial participation). Secondly, non-exploitation means that patients consent to voluntarily participate in an experiment rather than receiving personalized medical care directed at their best interest. Furthermore, given the distinction (and potential conflicts) between clinical trials and medical therapy, it is ethically undesirable for physician-investigators to enrol individuals in their studies with whom they have an ongoing doctor-patient relationship.

Possible advantages of this paradigm are related to methodological reasons in favour of PCTs with respect to active-controlled trials, especially when they are designed to test the "noninferiority" of treatment. PCTs, in fact, permit rigorous testing with less cost than active-controlled trials, and they expose fewer research participants to potentially toxic or ineffective experimental treatments. This datum does not mean to give science priority over ethics, as scientific validity is an essential requirement of clinical research.

6.4 A Critical Appraisal of the Non-Exploitation Paradigm

In my opinion, the proposal of the non-exploitation paradigm is too vague to guarantee sufficient protection of research subjects. In response to Miller, I argue that clinical research is a branch of clinical medicine that has been accorded the aim to test the safety and efficacy of unapproved drugs and novel therapies. Thus, the dominant goals of clinical research and clinical care may differ.

However, having the goal of obtaining scientific information does not mean that the physician-investigator should forget his/her own predominant duty of clinical care (Steinberg 2002). Because of the scientific goals of their activity, clinical investigators have not been accorded broad immunity from the ethical standards of clinical practice in general. In fact, if a physician treats a patient with either an accepted or an experimental therapy, a physician-patient relationship is established that obliges the physician to care for that patient. No exception is made for patients who are research subjects. Investigators who are physicians cannot withdraw from their ethical obligations merely because they are attempting to answer an important research question. Rather, the degree to which investigators can deviate from the ethics of clinical care should be limited to what is compatible with their therapeutic obligations. On the other hand, patients themselves, agreeing to participate in clinical investigations, do not relinquish the right to optimal medical care.

What makes it ethical to conduct an RCT comparing a new treatment with a standard treatment, but not with a placebo, is that experts in the clinical community are uncertain or in a state of disagreement about whether the new treatment is or is not better than standard therapy. Of course, if after the data is analysed, it is recognized that some participants in a therapeutic trial did not receive what ultimately proved to be optimal care, the investigators cannot be held morally responsible, because they could not have known in advance which arm of the study would be the optimal one.

On the contrary, attempting to justify a study by saying that it does not cause too much harm to too many people fails to take account of the physician-investigator's responsibility to each individual patient or subject. That would mean a betrayal of the therapeutic beneficence that physician-investigators have to each research participant. Therefore, as there is a therapeutic obligation, even in the context of RCTs, it should be considered wrong per se to use placebo controls that involve withholding proven effective treatment. That does not mean that PCTs are never an appropriate design (Cranley Glass and Waring 2002, International Conference on Harmonization 1996, World Medical Association 2000, World Medical Association 2002, World Medical Association 2008). Instead, there are some circumstances in which PCTs are ethically acceptable based on allowable risk. Some competent patients, for example, might be altruistic enough to refuse optional/unnecessary treatment for a minor condition in order to participate in research. If, as is the case with many minor medical conditions, no treatment is an accepted therapeutic option, then a PCT is consistent with clinical equipoise and may ethically proceed (Freedman 1990).

Physician-investigators must assure themselves that a state of clinical equipoise exists prior to mounting a clinical trial in order to assure that patients seeking care will not be disadvantaged by their random assignment to any trial arm. Ethical trial design requires that each prospective patient receives an "individualised assessment" of the suitability of participation in the trial (Weijer 2002).

It has also been argued that PCTs, in the face of proven effective treatment, lack scientific and clinical merit (Freedman et al. 1996a, b). That is because the purpose of RCTs have the ultimate aim of improving treatment (and not only introducing into the market another analogous medication!); therefore, we want

to know whether the new treatment is better than standard therapy (or at least as good as this one), not whether it is better than "nothing" (no treatment). The "non-inferiority" design answers to industries' interest instead of to patients' interest. Scientific validity (hypotheses of superiority of a new drug) is itself an essential ethical requirement of clinical research. No person should be subjected to the risks of research participation in studies that lack scientific validity. Both the arguments from therapeutic obligation (invoking clinical equipoise) and from scientific and clinical merit establish that PCTs are unethical whenever they evaluate treatments of conditions for which proven effective treatments exist, and not only when they do not expose research participants to excessive risks from placebo assignment (non-exploitation of research subjects).

6.5 The Ethics of the Declaration of Helsinki

Some authors (Rothman and Michels 1994) appealed to the Declaration of Helsinki in support of the claim that PCTs are unethical whenever they are used to evaluate new treatments for conditions when proven effective treatments exist. In fact, the Declaration of Helsinki (2008)—the cornerstone of research ethics—reminds the physician-investigator of their therapeutic duty.

Table 6.1 shows a comparison between the version of 2000 and 2008 in order to underline the relevance given to the therapeutic principle in the last version of the Declaration as well.

As we know, the objectives and principles of the Declaration were framed especially to protect human subjects in research in response to past abuses. However, the framework put in place to protect subjects has been criticised as paternalistic and for failing to address the full scope of ethically responsible research. Indeed, much has changed in the nature of research and bioethical thinking since the Declaration was conceived, so its periodic revision provides an opportunity for debate about its objectives and principles (Goodyear 2008). Concerns were also expressed that cumulative changes represented a shift towards protecting the efficiency of research at the expense of the protection of human subjects. Perhaps nowadays, the majority of clinical trials are primarily designed for marketing purposes; this fact should raise both the ethical and scientific question about the validity in continuing with currently standard protocols—and not only because of their placebo components (Healy 2002).

Generally, according to the Declaration of Helsinki, PCTs are unethical whenever they are used to evaluate new treatments for conditions when proven effective treatments exist. The 2002 "Note of Clarification" issued by the World Medical Association (WMA) on the use of placebo controls marked a fundamental departure from the previous revisions of the Declaration of Helsinki (1996 and 2000), which clearly posed an absolute prohibition of placebo controls to test the efficacy of new treatments when proven effective treatments exist for a given condition (see Boxed Text 6.1). Despite heated debate, the WMA has stood firm on the principle of not withholding effective interventions in its most recent revision of 2008.

Table 6.1 The Declaration of Helsinki: comparison between the version of 2000 and 2008

Declaration of Helsinki 2000	Declaration of Helsinki 2008
DH 2: It is the duty of the physician to promote and safeguard the health of people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty	DH 3: It is the duty of the physician to promote and safeguard the health of *patients, including those who are involved in medical research*. The physician's knowledge and conscience are dedicated to the fulfilment of this duty
DH 3: The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care *which might have the effect of weakening the physical and mental condition of the patient.*"	DH 4: The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that "A physician shall act in the patient's best interest when providing medical care."
DH 5: In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society	DH 6: In medical research involving human subjects, the well-being of the individual research subject *must* take precedence over all *other interests*
DH 15: Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent	DH 16: Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. *Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.* The responsibility for the *protection* of research subjects *must* always rest with the physician or other health care professional and never the research subjects, even though they have given consent
DH 28: The physician may combine medical research with medical care only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects	DH 31: The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and *if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects*

Boxed Text 6.1 Comparisons between the Declaration of Helsinki of 1996, 2000 and 2008, and the Note of Clarification of 2002

Declaration of Helsinki 1996: In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists. (part II, n. 3)

Declaration of Helsinki 2000: The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists (para 29).

Note of clarification 2002: […] that extreme care must be taken in making use of a placebo-controlled trial and that general this methodology should only be used in absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not subject to any additional risk of serious or irreversible harm […].

Declaration of Helsinki 2008: The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists, or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option (para 32).

However, the ethical guidance offered by the Declaration of Helsinki is still debated nowadays (Goodyear et al. 2007). Some authors (Rothman and Michels 1994) pointed to the regulatory policy of the United States Food and Drug Administration (FDA) as a major reason for the continued unethical use of placebo controls.[2]

[2] On this topic, see also Anna Westra's Chap. 12 in this volume.

Certainly, the Declaration's life and its power of protecting research subjects was further threatened when the US FDA on 27 October 2008 (Department of Health and Human Services FDA 2008) formally removed the requirement for trials conducted outside of the USA to comply with it. The FDA's proposal would mandate only that the submitted studies be consistent with the Good Clinical Practice (GCP) guidelines. However, the GCP guidelines were developed to mainly address procedural issues, not ethical ones. Actually, the FDA had already evaded the 2000 modifications to the Declaration of Helsinki, by declaring in 2001 that its reference would not have been to the current version, but to the weaker 1989 version. The FDA's concerns have focused on two areas, both absent from the GCP guidelines. Concerning placebo use, the FDA complained that the language in the 2000 Declaration precludes the use of placebos in studies of minor conditions. The FDA has also argued against the requirement in the Declaration that effective drugs be provided to all study participants at the conclusion of the research. Both these topics have major implications, especially for research in resource-poor nations (Goodyear et al. 2009; Kimmelman et al. 2009; Rennie 2009).

6.6 Concluding Remarks

As the FDA regulates the largest drug market in the world, I am concerned that its replacement of the Declaration of Helsinki with a less morally authoritative document may undermine international ethical standards for human medical research. This is why I suggest that all professional associations have a responsibility to foster an international culture of ethical research and to scrutinise that ethical reasoning is as central to research as it is to care. Specifically, I argue that the appeal to the principle of clinical equipoise should seriously been taken into account. In fact, the moral insight in the field of human medical research should consider that: (1) the therapeutic obligation has a relevance superior to testing scientific hypotheses also in the field of clinical investigation; and (2) physician-investigators do have a therapeutic beneficence obligation to each research participant (not simply an obligation not to exploit participants for the sake of scientific investigation).

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Chapter 7
Biomedical Research in Developing Countries and International Human Rights Law

Ilja R. Pavone

7.1 Background

Biomedical research is aimed mainly at discovering new drugs and vaccines, and enhancing health systems. It is often carried out in developing countries, where infectious diseases (in particular, HIV/AIDS, malaria and tuberculosis) are the major cause of death and have the dimension of a pandemic.[1] It is a fact that Goal 6 of the UN Millennium Development Goals (MDGs) is addressed to halt and reverse the spread of HIV/AIDS and other major diseases by 2015.[2]

Within the general process of globalization, the spread of research during the last decade has produced a shift of clinical research from the public to the private sector, and investment of pharmaceutical companies has focused on research and therapy with high economic returns on that investment. In such a context, clinical trials on tropical and/or poverty-related diseases (such as malaria, tuberculosis, HIV/AIDS) are of little interest to drug companies.

Furthermore, experimentations carried out in developing countries often contribute to developing new drugs which satisfy the interests of the sponsor country

[1] There are several explanations of this trend to transfer clinical trials (mainly Phase III-IV) to developing countries. First of all, drug companies can obtain substantial cost savings by conducting trials in developing countries. A first-rate academic medical centre in India, for instance, charges between $ 1,500 and $ 2,000 per case report, less than one tenth of the cost at a second-tier centre in the US. According to the FDA registry as of January 2011, approximately 30% of the clinical trials of the biggest US pharmaceutical companies are carried out in developing countries (Sub-Saharan Africa, South America, South East Asia) and in States of Eastern Europe (www.fda.gov/).

[2] United Nations, General Assembly Resolution 55/2 of 8 September 2000.

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and remain unavailable to the hosting countries. The conduct of clinical trials in low-income States has, therefore, raised a huge debate.

The ethical concerns regarding the conduct of the trial (the standard of care issue) and the end of the trial (sharing of benefits) have been translated into international guidelines, which are, however, not legally binding upon States. Some developing countries, such as Brazil, Kenya and South Africa, recently "codified" these ethical problems into legislations containing specific legal provisions on such matters.

The aim of this paper is to evaluate the ethical and legal issues concerning clinical trials carried out in developing countries. In particular, it analyses existing international standards concerning four themes that are relevant to this topic: (1) Informed consent; (2) double-standards; (3) use of placebo in clinical trials; and (4) post-trial obligations. This work concludes with some reflections on the need to guarantee additional legal safeguards to research participants considered as belonging to vulnerable groups involved in clinical trials.

7.2 International Human Rights Law and Biomedical Research

The provisions contained in human rights treaties particularly related to medical ethics are those requiring respect for human dignity and equality, the right to life, the prohibition of torture or cruel, inhuman or degrading treatment or punishment, non-discrimination, freedom from arbitrary interference with private life, and progressive realisation of the human right to a standard of living adequate for health and medical care (Annas and Grodin 1996).[3] In the same category is the human right to share in scientific advancement and its benefits, contained in article 27 of the Universal Declaration on Human Rights of 10 December 1948, and in article 15 (b) of the UN International Covenant on Economic Social and Cultural Rights (ICESCR) of 16 December 1966 (entered into force on 3 January 1976).

[3] The right to health is foreseen in several international treaties and declarations. The Preamble of the WHO Constitution underlines that the enjoyment of the highest attainable standard of health is a fundamental human right. The ICESCR establishes in Article 12 the right to enjoy the highest attainable standard of health through steps including: (1) Provisions for reducing stillbirth rate, childhood mortality, and development of the child; (2) improvement of environmental and industrial hygiene; (3) prevention, treatment and control of epidemic, endemic and other diseases; and (4) creation of conditions assuring all medical services and attention. The African Charter on Human and Peoples' Rights of 1981 foresees in Article 16 the "right to enjoy the best attainable state of health through necessary measures to protect health and ensure medical attention to the sick". Similar provisions are also contained in the American Declaration of the Rights and Duties of Man of 1948 (Article XI), the European Social Charter of 1961 (Article 11), the Additional Protocol on Economic, Social and Cultural Rights to the Inter-American Convention of 1988 (Article X), the UN Convention on the Rights of the Children of 1989 (Article XXIV), the Council of Europe Convention on Human Rights and Biomedicine of 1997 (Article III), and the UN Convention on the Rights of People with Disabilities of 2006 (Article XXV).

In particular, it is commonly accepted that unlawful human experimentation is an international crime in the context of war, and is deemed a war crime (Bassiouni 2003), but there is no specific proscription against this practice in time of peace, save for when it rises to the level of genocide or crimes against humanity. It is, therefore, part of war crimes during armed conflicts, and it also falls within the meaning of torture.[4] Quite relevant to the discussion at stake is the draft convention for the prevention and suppression of unlawful human experimentation, which could have been a logical progression from the Nuremberg Code and the Helsinki Declaration. It was presented by M. Bassiouni and considered in 1984 by the UN Sub-Commission on Prevention of Discrimination and Protection of Minorities, but was not eventually translated into a treaty.

HIV/AIDS and other pandemics are issues of development and are related to poverty, as outlined by the UN Secretary Ban Ki Moon.[5] Infectious diseases are spreading in developing countries where the right to health care is not adequately guaranteed. From this viewpoint, the central question is the exact content of the right to health care under international human rights law.[6] The answer to this question is very important in our discussion, because the right to health care encompasses all the ethical issues surrounding biomedical research in developing countries, including the standard of care debate.[7] Many scholars argue that the content of the right to health care is unclear, because its level of protection depends on several factors, such as health needs and available resources (Yamin 2009). The term "minimum core obligation approach" emphasises in a better way

[4] All four Geneva Conventions of international humanitarian law of 12 August 1949 list among the grave violations, which all parties are required to punish, "wilful killing, torture or inhuman treatment, including biological experiments". The 1998 Rome Statute of the International Criminal Court defines "war crimes" in Article 2 as: "Grave breaches of the Geneva Conventions of 12 August 1949, namely, any of the following acts against persons or property protected under the provisions of the relevant Geneva Convention: […] Torture or inhuman treatment, including biological experiments; [and] wilfully causing great suffering, or serious injury to body or health". In addition, Article 2(b) lists the following as serious violations of the laws and customs applicable in international armed conflict: "Subjecting persons who are in the power of an adverse party to physical mutilation or to medical or scientific experiments of any kind which are neither justified by the medical, dental, or hospital treatment of the person concerned, nor carried out in his or her interest, and which cause death to or seriously endanger the health of such person or persons."

[5] SG/SM/11004/GA/10595 AIDS/131 of 21 May 2007. See, also, Report of the Secretary-General, Uniting for Universal Access: Towards Zero New HIV Infections, Zero Discrimination and Zero AIDS-Related Deaths, 28 March 2011, A/65/797.

[6] The right to health care is a social right from which stem some duties the States have towards their citizens. It must not be confused with the right to health that, as outlined by Roscam Abbing in 1979, can never be obtained, as it implies the right of everybody to a given god which cannot be formulated objectively.

[7] The term "standard of care" can be defined as "the nature of the care and treatment that will be provided to participants in research". See National Bioethics Advisory Commission (NBAC) (2001), Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendation of the NBAC.

the governmental responsibility to protect its community from the further spread of infectious diseases, such as HIV/AIDS (Fidler 2000). In this regard, the content of the right to health care has been increasingly defined and now explicitly includes the availability and accessibility of prevention of sexual transmitted diseases, treatment, care, and support for children and adults.[8]

However, currently, any international treaty specifies that the right to health care includes the right to receive the same standard of care and treatment as would participants in the country sponsoring the research, and the right to receive post-trial treatment. Many scholars say that human rights treaties and declarations fail to encompass these topics on the right to health care, and they are not even sufficient to prevent physicians and researchers from experimenting on human subjects without their voluntary informed consent (e.g. de Groot 2005).

7.3 Overview of International Rules on Biomedical Research

More than a decade ago, Marcia Angell (1997) asked whether ethical standards should be substantially the same everywhere, or is it inevitable that they differ from region to region, reflecting local beliefs and customs.

It is widely accepted today that all research subjects are entitled to minimum guarantees that are transnational and non-negotiable due to their condition of vulnerability (Morawa 2003). The realisation of these entitlements is, of course, a separate matter. However, institutional mechanisms for promulgating and applying human subject protections have advanced considerably, hurried on by several scandals and major public inquiries. Industrialized countries use formal ethics review committees and similar criteria to evaluate any government-funded study involving human subjects, wherever and however it is conducted. Among the minimum guarantees, formalised in the Declaration of Helsinki (DH), adopted by the World Medical Association (WMA) in its last version in 2008 and reiterated in international guidelines, are the valid scientific design of the clinical trial and the conduct of it by qualified physicians; and the reasonable balance between the predictable risks and foreseeable benefits to the subjects or others, with the specific provision of the moral primacy of the human being. Furthermore, it is commonly accepted that all study subjects must consent to participate through a decision that

[8] With reference to HIV/AIDS, according to the UN General Committee on Economic, Social and Cultural Rights (General Comment no. 14 of 11 May 2000), Article 12.2 (C) of the ICESCR "requires the establishment of prevention and education programs for behavioural-related health concerns such as sexually transmitted diseases, in particular HIV/AIDS and those adversely affecting sexual and reproductive health, and the promotion of social determinants of good health and the promotion of social determinants of good health, such as environmental safety, education, economic development and gender equity. […]. The control of disease refers to States' individual and joint efforts to, inter alia, make available relevant technologies, using and improving epidemiological surveillance and data collection on a disaggregated basis, the implementation or enhancement of immunization programs and other strategies of infectious diseases control".

must be made without duress or coercion and only after details of the study are provided. When investigators from one country conduct research in another country, it is appropriate to add to this list of minimum guarantees the requirement that the research must hold the promise of direct, tangible and significant benefit to the host country population, if not to the study subjects themselves. However, determining whether such benefits are likely to accrue can be problematic, because researchers and government officials in the host country will often have a vested interest in ensuring that the research proceeds.

The number of international standards on biomedical research with a particular focus on developing countries is steadily increasing. There are considerable differences between the institutions involved: Some of them act at an intergovernmental level (World Health Organization—WHO, UNESCO, Council of Europe—COE, European Union—EU), others at a non-governmental level (Council for International Organizations of Medical Sciences—CIOMS, World Medical Association—WMA). These competing actors give rise to coordination problems and overlapping mandates and often pursue different interests and goals. Furthermore, many governments and authorities in developing countries are overstrained by this multiplicity of external actors and different modes of governance. Is this parallel structure an asset or a weakness? In reality, could it contribute—through improved coordination—to better management?

The status, scope and contents of international documents also vary. The DH is the fundamental international document in the field of ethics in biomedical research and has influenced the formulation of international, regional and national legislations and codes of conduct. The DH confirmed and established the key pillars for the ethical review of medical research (voluntary consent of the research participant; independent review of the project; assessment of the risk; and involvement of competent researchers of integrity and research merit) (Chalmers 2004). Other international standards include the International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines, the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by CIOMS and WHO in 1993 and amended in 2002 (Legemaate 1994), the UNESCO Universal Declaration on Bioethics and Human Rights of 19 October 2005 (Faunce 2005), and the COE Additional Protocol to the European Convention on Human Rights and Biomedicine, concerning Biomedical Research, of 25 January 2005 (entered into force on 01 September 2007) (Pavone 2009a, b).

This may create confusion and give rise to problems of overlapping and fragmentation, in particular where they do not support and complement each other. In fact, as pointed out by Gevers (2001), the central issue in the field of biomedical research is not related to the lack of international guidance, but rather to the proliferation of codes, guidelines and declarations, that do not facilitate the establishment of a common, universally accepted standard of care.

The DH and the Universal Declaration on Bioethics are the most authoritative guidelines on issues related to human experimentation. Although they are not legally binding upon States, they are generally regarded as soft law. This term

refers to rules which are neither strictly binding nor completely void of any legal significance because these may turn into customary law if supported by general and consistent State practice (*diuturnitas*) with the sense of being obliged to do so (*opinio juris*) (Marchisio 2000, 165; Shaw 2008). Some scholars explain that declarations may

> […] catalyse the creation of customary law by expressing in normative terms certain principles whose general acceptance is already in the air […] and thereby making it easier and more likely for States to conform their conduct to them. (Szasz 1992)

The DH, for instance, has been often been relied upon by national courts as a source of "the accepted custom or practice of nations". The principles laid down in the DH have been invoked in several claims brought by individuals against pharmaceutical companies in the US and in Canada. The courts, on their side, have used the DH as an interpretation instrument of the national laws and regulations in order to verify their compatibility with international standards (Plomer 2005). The DH is also recalled in the preamble of international treaties and declarations and in several local laws on bioethics.[9]

In conclusion, although the two declarations are not treaties, they are potentially binding in the long-term and are having a concrete influence on the legislative process of developing countries. Some scholars argue, indeed, that the UNESCO Declaration on Bioethics when adopted by an intergovernmental organization has an upgraded legal value compared to the DH, which was drafted by a non-governmental organization not representing any State. It means that for some scholars, the DH is a merely a code of conduct, similar to a deontological code (Andorno 2007).

7.4 Key Issues in Biomedical Research in Developing Countries

7.4.1 Informed Consent

The issue of consent to medical treatment and experimentation arose in the medical community after World War II and the atrocities committed by Nazi doctors. The Code of Nuremberg, adopted in 1948, was the first international code containing the requirement of consent (Annas and Grodin 1992). This principle is then clearly stated in Article 7 of the UN International Covenant on Civil and Political Rights (ICCPR) of 16 December 1966, (entered into force on 23 March 1976), which expressly prohibits medical or scientific experimentation without the free consent of the person concerned. According to the United Nations Human Rights Committee (HRC), the monitoring body of the ICCPR, this disposition should be interpreted as providing:

[9] See, for instance, the Preamble of the Universal Declaration on Bioethics and Human Rights.

> […] special protection in regard to such experiments in the case of persons not capable of giving valid consent, and in particular those under any form of detention or imprisonment. Such persons should not be subjected to any medical or scientific experimentation that may be detrimental to their health. (CCPR General Comment No. 20. General Comments)

It implies a duty of the States under international law to adopt adequate measures aimed at guaranteeing special protection in the field of medical experimentation to the vulnerable groups identified by the HRC (in particular, prisoners and people deprived of their liberty) (Bassiouni et al. 1981). The requirement of the informed consent to medical treatment was widely recognized at that time in national and international law. In particular, Article 24 of the Un Convention on the Rights of the Child of 20 November 1989 (entered into force on 2 September 1990) stipulates that the States

> […] recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health,

going on to provide that

> all segments of society, in particular parents and children, are informed […] of child health and nutrition.

The UN Convention on the Rights of People with Disabilities of 13 December 2006 (entered into force on 03 May 2008) recognises the right of the disabled persons to express their informed consent to any medical treatment (art. 25, d).

At a regional level, the Charter of Fundamental Rights of the European Union, proclaimed in Nice on 18 December 2000 (now part of the Lisbon Treaty and therefore binding), provides moreover that

> everyone has the right to respect for his or her physical and mental integrity

and that in the fields of medicine and biology, amongst other things, in particular,

> the free and informed consent of the person concerned, according to the procedures laid down by law

must be respected (art. 3). In the framework of the African Union, the provision of Article 4, para. 2, h, of the Protocol to the African Charter on Human and Peoples' Rights on the Rights of Women in Africa of 11 July 2003 (entered into force on 13 October 2005) prohibits all medical and scientific experiments on women without their prior informed consent (art. 4, f).

The principle of informed consent is also foreseen in all the international treaties and guidelines concerning bioethics[10] and is contained in many legislations of

[10] Article 5 of the Convention on Human Rights and Biomedicine provides that: "An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it"; articles 13 and 14 of the Additional Protocol to the Biomedicine Convention on Biomedical Research establish further safeguards concerning the information and the consent of research participants, respectively.

western countries as a core principle of biomedical research. In Italy, for instance, the Constitutional Court recognized informed consent as a fundamental human right of the patient,[11] and some scholars say that this principle has emerged or is emerging as a general principle of international law under Article 38 (1) (c) of the Statute of the International Court of Justice or customary rule (Dickens 2001). Nevertheless, as underlined by Meier (2003), there is not yet a widespread or consistent State practice supporting such a right. He also argues rightly that only a multilateral universal treaty clearly establishing the right to informed consent could facilitate the achievement of a widespread and consistent State practice.

Nevertheless, the principle of informed consent in developing countries needs additional requirements and safeguards due to the condition of illiteracy and poverty of most of the research participants. Unfamiliarity with the concept of modern medicine and informed consent creates problems concerning the effective level of comprehension of the information received by the research participants in developing countries: How "effectively informed" could be the consent of an illiterate Swahili-speaking person living in Sub-Saharan Africa? In order to address this issue, the setting of an international standard requires further information to be provided to research participants belonging to vulnerable groups in order to first of all acquire a genuine consent.[12] To obtain genuine consent, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made. It should include such matters as the nature and purpose of the research, the procedures involved, and the potential risks and benefits.

In addition, they should provide that when, because of communication difficulties, investigators cannot make prospective subjects sufficiently aware of the implications of giving adequately informed consent to participation, the decision of each prospective subject on whether to consent should be elicited through a reliable intermediary, such as a trusted community leader. Article 6, para. 3, of the UNESCO Declaration affirms, for instance, that in appropriate cases of research carried out on a group of persons or a community, additional agreement of the legal representatives of the group or community concerned may be sought. In no case should a collective community agreement or the consent of a community leader or other authority substitute for an individual's informed consent. This provision could raise some criticism because research participants are

[11] Judgement no. 438 of 2008, para. 4: "Informed consent, understood as an expression of the informed acceptance of the medical treatment proposed by the doctor, has the status of a full-scale right of the person and is grounded in the principles expressed in Article 2 of the Constitution, which protects and promotes fundamental rights, and Articles 13 and 32 of the Constitution which provide, respectively, that 'personal freedom is inviolable' and that 'nobody may be forcefully submitted to medical treatment except as provided by law.'"

[12] See the UNESCO Declaration on Bioethics, COE Additional Protocol on Biomedical Research, CIOMS Guidelines, WMA Declaration of Helsinki.

considered as incapacitated adults, unable to take decisions on their own. The role of the community leader in the process of obtaining consent is also specifically recognized in some developing countries' guidelines on biomedical research.[13]

7.4.2 Double Standards

7.4.2.1 The Standard of Care Debate

The practice of pharmaceutical companies to carry out phase III clinical trials, otherwise prohibited in the sponsor countries, in developing countries raised the issue of double standards in clinical trials (Lurie and Wolfe 1997, Macklin 2004). Examples of such procedures in experimentations in developing countries are not difficult to find (Kiatboonsri and Richter 1998).

This problem is strictly related to the standard of care debate, which focuses on whether research participants in the control group of a research trial should be provided with an universal standard of care, regardless of where the clinical trial is carried out, or only with the treatment available in a defined region (Van der Graaf and van Delden 2009). The central issue is why or if a lower standard of treatment for poor people living in developing countries should be admitted. We may find various responses to these issues. Some scholars argue that it should be ethically and legally admitted because successful research will bring benefits and progress to that society, and constraints to it may have a negative impact on these countries in the medium- and long-term (Wertheimer 2010). However, when we evaluate this argument, we should keep in mind that this kind of research is often conducted on diseases and therapy diffused in the sponsoring countries with high economic return on investment (Ravinetto 2010).

On the other hand, as outlined by Angell (1988), providing a lower standard of care is not ethically admissible because it is equivalent to a sort of exploitation, and physicians have a moral duty to provide a universal standard of care.

We could also consider this practice as contrary to the fundamental human rights contained in international declarations and treaties. In particular, the lower standard of treatment provided to these patients could be considered as a violation of the principle of non-discrimination and of the right to the enjoyment of the highest attainable standard of physical health, as expressed in Articles 3 and 12 of the UN Covenant on Economic, Social and Cultural Rights and in several treaties and declarations. In this regard, one should underline that, as affirmed by the European Court on Human Rights, each different treatment should not necessarily

[13] See, for example, Paragraph IV (3e) of the Brazilian Resolution No. 196/96 on Research Involving Human Subjects, which states that "in communities with a different culture, including Indigenous communities, prior consent must be obtained from the community through its leaders, without foregoing, however, efforts to obtain individual consent."

amount to unequal treatment and discrimination.[14] Discrimination may arise when States, without an objective and reasonable justification, fail to treat differently persons whose situations are significantly different.[15] Exceptions to this principle are admissible only if there are objective, reasonable justifications for the different treatment.[16] Researchers, for instance, may seek to determine whether a new treatment for a disease is better than the one currently available in a developing country. To do this, they want to compare the new treatment with the current treatment that is available within that country, rather than with another, but much more expensive treatment that is available in developed countries. It is not yet clear whether this practice could be considered as coherent with human rights standards.

7.4.2.2 Legal Standards

Shared principles concerning the prohibition of double standards are emerging at an international level if we look at existing guidelines under a comparative point of view. The DH is the primary source of guidance on which the majority of other guidelines are based. It is, therefore, our starting point. The 2008 version of the DH establishes that the benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best proven current method (para. 32). In this regard, it is interesting to note that the US Food and Drug Administration (FDA) does not apply the DH, but relies on the Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products (ICH-GCP) (Comoretto 2010).[17] Additionally, the Joint United Nations Programme on HIV/AIDS (UNAIDS), a subsidiary body of the General Assembly devoted to the fight against HIV/AIDS, uses the term "highest attainable standard of care", attainable in the host country (2011, Political Declaration on HIV/AIDS: Intensifying our Efforts to Eliminate HIV/AIDS) as the minimum standard which should be provided to the control group.

CIOMS Guidelines establish, on their part, several principles prohibiting double standards. Firstly, Guideline 15 affirms that international research protocols should undergo an ethical review in both States and if it is rejected in one country, the research should not be conducted. Furthermore, Guideline 8 states that if research can be conducted in the developed country, then it should not be carried out at all in a developing country. It means that one can perform research on people

[14] Camp and Bourini v. The Netherlands, n. 28369/95, ECHR 2000-X, para. 37.

[15] Thlimmenos v. Greece [GC], no. 34369/97, § 44, ECHR 2000-IV.

[16] Pretty v. United Kingdom, Final, 2346/02, ECHR, 2002, para. 32.

[17] This is clearly established in the Fed Reg April 28, 08, 22800-16, 27/X/08.

belonging to an underdeveloped community only in the absence of a valid alternative.[18] CIOMS reinforces this principle, declaring that a clinical trial performed in a developing country or on a vulnerable group should not only be approved in both countries, but it should also be carried out simultaneously.

The commentary to Guideline eight states that Phase I drug studies and Phase I and II vaccine studies should be conducted only in developed communities of the country of the sponsor. In general, adds the commentary, phase III vaccine trials and phase II and III drug trials should be carried out simultaneously in the host community and the sponsoring country; they may be omitted in the sponsoring State only on condition that the drug or vaccine is designed to treat or prevent a disease or other condition that rarely or never occurs in the sponsoring country.

The UNESCO Declaration on Bioethics and Human Rights contains several principles that indirectly treat this topic, such as the benefit harm balance (art. 4), the respect for human vulnerability and personal integrity (art. 8), equality, justice and equity (art. 10), and non-discrimination (art. 11). It is not clear if Article 21 of the Declaration, regarding transnational practices, applies to clinical trials in developing countries. Article 21, lett. a, affirms that States, both public and private institutions, should assure that any transnational practice is consistent with the principles set out in the Declaration. The most important disposition regards, nevertheless, the necessity of a double ethical review, which must be carried out both in the host State(s) and in the funding State (art. 21, lett. b). In practical terms, this article requires that all research projects be submitted for independent examination of their scientific merit and ethical acceptability in each State involved in the clinical trial.

A clear and binding prohibition of double standards is foreseen in Article 29 of the Additional Protocol to the Biomedicine Convention on Biomedical Research, which establishes that sponsors or researchers that plan to undertake or direct research in a third State shall ensure that the research project complies with the principles of the Additional Protocol (in addition to complying with all the conditions applicable in the State where the research is carried out). In addition, Articles 9 and 10 of the Additional Protocol concern independent examination of ethics committees and the independence of ethics committees. These concern informed consent, confidentiality, protection of those unable to consent, balance between risks and benefits, and ethical review of research projects.

At a European level, the EU has no direct competence on the regulation of research at large which is a matter of national competencies (Kervey and McHale 2004). However, the EU has competence for the marketing authorisation of medical products related to the single market, and established a common standard on clinical trials contained in the Directives nos. 2001/20/EC (Clinical Trials Directive) and no. 2005/28/EC (GPG Directive). They regulate the conditions

[18] Guideline 8 establishes that: "Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably in developed communities."

under which clinical trials of pharmaceutical products may be carried out within and outside the EU, and establish that European Standards (and those contained in the DH) should be respected when carrying out experimentations in developing countries (Baeyens 2002). These acts provide a legal framework for the review of a clinical trial dossier by the European Agency for the Evaluation of Medicinal Products (EAEMP) after the conduct of a trial. The EAEMP, in case of violation of the Clinical Trial Directive, can advise the EU Commission to refuse the marketing authorisation or can suggest the withdrawal of marketing authorisation already delivered by Member States. This mechanism is especially important for European companies doing their research in developing countries: The companies are in this way obliged to respect the European standards if they want to commercialize their products on the EU market.

7.4.3 Use of Placebo in Clinical Trials

7.4.3.1 The Moral Supremacy of the Human Being

Researchers, in an effort to obtain the fastest and most useful results, often conduct placebo-based clinical trials, whereby some research subjects receive the experimental new drug while others receive a placebo treatment, which is, in actuality, no treatment at all. Researchers argue that placebo-based trials in poor countries are necessary because the "best proven therapeutic treatment" will never be available to the population due to the cost of the technology, and the conduct of trials that may produce lower cost versions of a treatment justifies this type of research.[19] The placebo debate was raised by some clinical trials conducted in South Africa and Thailand on HIV-positive pregnant women providing them placebo in order to find a more economic and affordable treatment to prevent vertical transmission of HIV. The problem arose, in particular, because an effective treatment had already been available since 1994 (Annas and Grodin 1998).

The core principle of research ethics, according to which the interest of the individual shall prevail over the sole interest of science and of society (Parker 2010), is the key argument against placebo. It is based on the idea that one cannot justify endangering individuals for the sake of acquiring knowledge that may benefit society in general or future patients. This principle emerged in order to avoid repeating the past examples of misuse of research, where unethical research projects were justified for precisely this reason. This assumption is, however, problematic and controversial because, as some scholars have argued, all clinical trials involve a certain amount of risk for the research subjects, which is justified only in terms of possible future benefits (Helgesson and Eriksson 2011). It means

[19] Clinical trials are conducted in four phases: Phase I, carried out with healthy volunteers, phase II performed on a limited number of patients, phase III, performed on a large number of patients, and phase IV, performed after the product has been commercialized.

that it is difficult to understand in exactly what sense the interests of the individual shall be given precedence over science and society. In the case of placebo trials, the supremacy principle is being displaced by the utilitarian research goal to benefit a large number of patients in the future. In fact, one of the main arguments in favour of the use of placebo in clinical trials concerns the possibility of obtaining a faster, scientifically more reliable answer than the use of active controls, which would result in a substantial increase in expense, as well the loss of efficiency (Levine 1999).

The moral supremacy of the human being has been codified in international rules concerning biomedical research.[20] It has acquired a particular value in the Biomedicine Convention (art. 2). Now, according to its Explanatory Report, this principle should be understood as the main guiding principle of the entire Convention, rather than one of the assumptions of the treaty on a level with the others. The Convention clearly builds a hierarchy of principles and poses this concept as the ethical foundation of the treaty architecture.[21] One of the important fields of application of this thought concerns research. Nevertheless, the central issue is to determine who establishes what is the best interest of the individual. In the South African case, some HIV-patients—in disagreement with the ethical committee—considered their "best interest" was to receive ART during a clinical trial even if, at the end of the experimentation, the drug company had assumed no post-trial obligation. In fact, being enrolled in a two-year study was an opportunity for them to increase their life expectancy. The ethics committee, that firstly had refused its authorisation, was eventually forced to concede it under the pressure from the research subjects.

7.4.3.2 The Legal Responses to the Placebo Scandals

The placebo scandal led to the most heated debate on the ethics of clinical trials since the 1970s which caused the revision of WMA and CIOMS documents (Studdert and Brennan 1998). The 2000 version of the DH and the revised CIOMS Guidelines of 2002 contain several revisions. However, the main innovations are mainly contained in paragraphs 4, 6 and 32 of the 2008 version of the DH.[22]

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[20] See, for example, Article 3 of the Universal Declaration on Bioethics, and Article 2 of the ECB. Article 22 of its Explanatory Report states: "The whole Convention, the aim of which is to protect human rights and dignity, is inspired by the principle of the primacy of the human being, and all its articles must be interpreted in this light."

[21] Nevertheless, the Explanatory Report to the ECB has lowered the concrete application of this principle, specifying that the interest of the human being must "in principle" take precedence over science and society in the event of a conflict between them.

[22] Article 29 of the 2000 version of the DH provided that: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." The previous version also contained the reference to investigation for a "minor condition", that, combined with the minimal harm principle, would have implied the use of placebo only in trials with some analgesics, hypnotics, antihistamines, and antiemetics where the disease would have been minor.

In particular, paragraph 4 states the duty of the physician to provide the best standard of care to "patients, even those involved in biomedical research". The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best current proven intervention.

This rule originates from the concept of "highest attainable standard of care" enshrined in the UN Covenant on Economic, Social and Cultural Rights of 1966, which implies the individual right to the highest attainable standard of care and treatment. This provision contains, nevertheless, several exceptions: A placebo-controlled trial may be ethically acceptable only in the absence of a current proven intervention, or if is necessary for compelling and scientifically methodological reasons and does not imply any serious or irreversible harm for the patient.

UNAIDS Guidelines also establish in this regard that a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial only as long as there is no known effective HIV preventive vaccine.[23]

The inappropriateness of placebo control is generally affirmed by international guidelines, such as the DH and opinions of ethics committee (see, for example, the Advisory Opinion of the Italian National Bioethics Committee of 29 October 2010 on the Improper Use of Placebo). ICH[24] and CIOMS[25] guidelines, and COE[26] and

[23] UNAIDS "Ethical Considerations in HIV Preventive Vaccine Research (2000)". Guidance Point 11 states: "As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial". Guidance Point 16 specifies that: "Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of…circumstances listed. These circumstances include: the level of care and treatment available in the sponsor country, the highest level of care available in the host country, the highest level of treatment available in the host country (including the availability of antiretroviral therapy outside the research context in the host country), the availability of infrastructure to provide care and treatment in the context of research, potential duration and sustainability of care and treatment for the trial participant. In addition, UNAIDS/WHO Guidance 2007 establishes that the use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations (Article 15)."

[24] ICH, 2000, para. 2.1.3 establishes: "Where an available treatment is known to prevent serious harm (…) it is generally inappropriate to use a placebo control. Whether a particular placebo controlled trial of a new agent will be acceptable (…) when there is known effective therapy (…) is a matter of judgement." The guideline on "The Choice of a Control Group" (E10) affirms that "Whether a particular placebo-controlled trial is ethical may in some cases, depend on what is believed to have been clinically demonstrated and on the particular circumstances of the trials." "It should be emphasised that use of placebo or no-treatment control does not imply that the patient does not get any treatment at all."

[25] CIOMS Guidelines for Biomedical Research (1993) state that: "If there is already an approved and accepted drug for the condition that a candidate drug is designed to test, placebo for controls usually cannot be justified." (Commentary on Guideline 14).

[26] COE, 2005, Articles 23.2 and 23.3 state: "The use of placebo is permissible where there are no methods of proven effectiveness.".

EU[27] binding rules show an emerging *opinio juris* on the prohibition of placebo controlled trials in cases of availability of methods of proven effectiveness. Tragically, for the hundreds of children who have needlessly contracted HIV infection in experimentations conducted in the past that have already been completed, any such diffused *opinio juris* against double standards and placebo will have come too late.

7.4.4 Post-Trial Obligations and Benefit Sharing

7.4.4.1 The Ethical Debate

Much of the debate about the ethical issues surrounding clinical trials in developing countries has focused on the protection of research participants during the clinical trial. However, there are also important issues concerning the welfare of the human being in the post-trial stage. In many cases, the research yields a beneficial treatment which is never made available to the research subjects who have contributed to its success, nor to the greater population in the country where the research has been carried out. Pharmaceutical companies continually justify this reality by highlighting their inability to reconcile the cost of providing the drug with that population's capacity to pay for it, even at a reduced cost.

Many drugs and vaccines for tropical diseases are simply not affordable in developing countries. The cost of HIV antiretroviral drugs is, for instance, well beyond the means of most individuals and governments in developing countries.[28] Other drugs and vaccines, particularly those still under patent protection, are also prohibitively expensive in developing countries, limiting access to effective and safe pharmaceuticals. Furthermore, the possible impact of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) on access to drugs and vaccines in the developing world raises the issue of the role of national and international law in the development of pharmaceuticals and access to them (Pavone 2009a, b).

The underlying concern in the standard of care debate is the increasing access to medical treatment in the populations of developing countries. Many governments of developing countries have already made inroads towards providing cheaper drugs to populations who are most in need and, in several cases, pharmaceutical

[27] The Directive 2001/83/EC on the Community Code relating to Medicinal Products for Human Use, specifies that: "In general clinical trials placebo shall be done as controlled clinical trials and if possible, randomised; any other design shall be justified. The control treatment of the trials varies from case to case and will also depend on ethical considerations; thus, it may, in some instances, be more pertinent to compare the efficacy of a new medical product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo".

[28] According to WHO data, 5.25 million people (36%) of those in need in 2009 had access to ART in low- and middle-income countries.

companies have donated drugs to countries that are in dire need. However, most economists agree that this only provides short-term relief, because eventually the donated supply will be depleted, leaving the population in substantially the same position as before.

Post-trial obligations are an important component of international research ethics. The ethical and legal discussion on this topic arose largely from concerns about the exploitation of people in developing countries. The old understanding was that researchers' obligations would end when the study did. After the HIV trial in South Africa in the 1990 s, something changed in the ethical debate. Some accounts argue that not providing drugs once the trial has ended is a form of exploitation. Buchanan (1985) says that to exploit a person involves the harmful, merely instrumental utilization of her or his capacities for one's own advantage or for the sake of one's own ends. This definition recalls the Kantian assumption according to which exploitation occurs when one treats another instrumentally or merely as a means, and thus, placebo control trials (PCTs) that withhold proven effective treatment are exploitative. On this basis, the ethical justifications for post-trial obligations can be summarized as a compensation for harm and a duty to rescue.

Other scholars underline, indeed, that the argument founded on the concept of exploitation is much too simplistic, and a clear distinction should be made between harmful exploitation and mutually advantageous exploitation (divided in turn into consensual and non-consensual exploitation) (Sample 2003). Wertheimer (2010), for instance, argues that the participation in a clinical trial in the absence of alternatives and with the prospect of receiving no care is a benefit to the subject of the research and does not amount to exploitation. The case of the African short course AZT testing in the 1990s is a practical application of this argument. Due to the lack of post-trial access, the local ethics committee decided not to approve the research project; but activists and community members objected because they preferred access to the trial to no access at all. In particular, they argued that this trial might have helped them to demand access to ART from their government more systematically, and said that the trial might have helped them to buy time until ART would have been more readily available. It is evident that HIV-infected people in South Africa did not consider a short-term treatment, which could have prolonged their lives only for a couple of years, instead of no treatment at all, as a form of exploitation.

7.4.4.2 Legal Issues

Briefly analysed, the sharing of benefits debate is strictly related to post-trial benefits and poses several legal problems. Is there a legal duty of the pharmaceutical company that carried out a successful trial on a research subject in a developing country or of the national State to provide post-trial therapy? If yes, what kind of therapy? In the case of an HIV-positive research subject, should it include anti-retroviral drugs, such as AZT, and how long should it last: Five years,

ten years or until the death of the patient? Is it a collective right of the family of the patient or of the village community to obtain adequate health care assistance, and what happens if the outcome of the trial is not positive?

There is another topic which is unresolved: Who should evaluate what is in the best interests of a human being? An HIV-positive person in Sub-Saharan Africa without access to anti-retroviral treatment could consider the inclusion in a morally dubious clinical trial as being in their best interests. A person in the same condition in a western country which has a high standard of care could probably would not want to be included in a trial like this. In these cases, could the State be considered as the best judge of the subject's interests?

Under a human rights perspective, one could argue that the post-trial benefit obligation has already been foreseen through the right to the highest attainable standard health or the right to enjoy the benefits of scientific progress enshrined in universal human rights treaties. Such arguments are weak, because no consensus exists among States on the exact meaning of these terms.[29] In addition, even in the presence of such consensus, the mechanism of monitoring and implementation of cultural, economic and social rights is traditionally weak. They are usually compared with civil and political rights through the observation that civil and political rights are negative rights, requiring the States to refrain from certain acts in their treatment of individuals, while economic, social and cultural rights are positive rights, requiring governments to provide individuals with the conditions and resources necessary to satisfy the rights, depending on the resources available.[30]

However, several international guidelines recognise a right to post-trial therapy and a correspondent post-trial obligation by the drug company. The WMA Declaration of Helsinki dealt with post-trial obligations for the first time in the 2000 version, stating a right of the patient involved in a study to have access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. The 2008 version now states that researchers should describe post-trial access arrangements in the protocol and participants are entitled to be informed about the study outcome and to share in any benefits.

The UNESCO Declaration on Bioethics and Human Rights establishes that "when negotiating a research agreement, dispositions concerning the benefits of the research to the hosting country should be established" (art. 21, lett d). This disposition suggests elaborating prior agreements to access successful findings. It can be interpreted in two different ways. According to a first point of view, the negotiation process should involve the pharmaceutical company and competent local authorities (such as an ethics committee). The member of the ethics

[29] According to WHO Constitution, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

[30] Article 2.1. of the ICESCR provides that: "Each State Party to the present Covenant undertakes to take steps, individually and through international assistance and cooperation, especially economic and technical, to the maximum of its available resources, with a view to progressively achieving the full realization of the rights recognized in the present Covenant by all appropriate means, including particularly the adoption of legislative measures."

committee, who represent both the State and the research subject, should clarify the content of this agreement and, in particular, obtain the assurance that the outcome of research will be made "reasonably available" to members of the host population. According to another model, "the fairly beneficial approach", the host population should be directly involved in the negotiations through a process of collective informed consent (Langlois 2008). A possible compromise of this negotiation process could be to convince pharmaceutical companies to establish differential pricing schemes where companies would provide their products to developing countries at a fraction of the price the products are offered in developed countries. This too has its limitations, as even the reduced cost is often too burdensome for the populations of the developing countries. The struggle inherent in all of the international agencies' protocols is balancing the need to encourage and reward scientific research with the need to make medical technology available to developing countries. The WTO's TRIPS require all member countries to acknowledge patents held by pharmaceutical and biotechnology companies, and requires member States to pass laws that protect these patents. At first glance, the WTO's stance on international patents appears to protect companies and to reward their innovative efforts at the expense of needy populations who cannot afford to pay premium prices for patented products (Cadin 2004). However, the WTO's agreement contains an important provision which allows countries to produce generic versions of patented drugs in the case of a "national emergency", in which case, the patent holder is paid a fair royalty for what essentially amounts to permissive infringement.

Another issue concerns other types of post-trial obligations. Sponsors and researchers should provide information after the trial is over about the study findings, the participation in placebo or control group, and possible adverse events occurring years later.

UNAIDS/WHO Guidance 2007 establishes in Article 19 that researchers should inform trial participants and their communities of the trial results. During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and the country concerned should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country. A guideline related to HIV/AIDS is particularly important, because post-trial access for HIV/AIDS antiretroviral trials in developing countries is more challenging than other diseases in some respects, requiring expensive, life-long and potentially life-saving treatment in contexts that may lack the necessary health-care infrastructures. With regard to diseases other than HIV/AIDS, short-term treatment of acute illness or prevention modalities may be more feasible instead. Challenges remain for diseases that are chronic (e.g. diabetes), for which treatment occurs in tertiary care facilities (e.g. surgical intervention for heart disease), or requiring expensive and complicated treatment regimens for a period of time (e.g. cancer chemotherapy).

Similar dispositions have also been foreseen by CIOMS Guidelines. In particular, the obligation of the sponsor to make reasonably available for the benefit of the population or community concerned any intervention or product developed, or knowledge generated, as a result of the research is considered in Guideline 10. As CIOMS puts it, the research should be responsive to the health needs and priorities of the community in which it has to be carried out and:

> as a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing. (Guideline 10)

Exceptions to this general requirement should be justified and agreed to by all parties concerned before the research begins. As Schroeder (2008) says, the exact meaning of the term "reasonably available" is not clear. CIOMS does not provide any answer to this question; it only notes that the decision on the amount of post-trial obligations should be made on a case by case basis.

Guideline 21 notes that research sponsors are ethically obliged to ensure the availability of services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or a product developed as a result of the research reasonably available to the population or community concerned.[31]

It is obvious that the ability to provide post-trial access varies depending on the context, and researchers cannot do it alone when the demands are great. In addition, it is important to coordinate with the external source of care well in advance of the need for post-trial access, which could increase the chances that plans for post-trial access will endure. As underlined by Millum (2009), the justification for post-trial access is missing from this guidance. If we know why post-trial access should be provided, we will better understand who should provide it to whom. The justification may also help to determine what should be provided and for how long.

[31] Commentary on Guideline 21 specifies the content and scope of the moral obligation contained in the Guidelines. The Commentary states that obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn or to the host country, and for how long. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed arrangements should be specified in the consent process and document. It is evident that the communities concerned are involved in the negotiation process with the drug company "when appropriate", and it is the State that should represent their interests. In the reality of developing countries, where governments are often corrupt, a more incisive disposition concerning the role of the research participants in the deal should have been provided.

7.5 Concluding Remarks

On the basis of this brief overview, some conclusions can be expressed. First of all, as many scholars have observed, the proliferation of declarations, codes and guidelines on biomedical research risks create confusion, competition among these documents and overlapping. The best option would be the adoption of a single multilateral treaty on medical experimentation, clearly defining a single universal standard of care, inspired by the draft convention presented by Bassiouni in the 1980s.

Secondly, several levels of protection have been established. With reference to ethical issues concerning biomedical research, an *opinio juris* among member States is progressively emerging on some common principles, such as informed consent, the principle of respect for human dignity and the principles of non exploitation, non discrimination and non-instrumentalisation. More detailed principles on a minimum standard of protection for research participants in developing countries have also been affirmed. These include a general condemnation of double standards, of placebo trials if an effective treatment already exists and a recognition of a post-trial obligation. These principles are strictly related to fundamental social human rights, such as the right to equal treatment in health care, to share the benefits and to the concept of the supremacy of the interest and welfare of each single human being over science and society.

However, despite the prestige and expertise of the intergovernmental and non-governmental organizations which drafted and translated the aforementioned principles into codes, their end-product is not binding upon researchers, private companies and States. In practical terms, the implementation of these principles is weak and relies on the goodwill of States. Yet, with reference to the issue of benefit sharing, data show that not all researchers and sponsors respect post-trial obligations that have been fulfilled mainly through coordination with other services that provide care. In studies on HIV/AIDS, companies provided ART for a short period of time, including up to commercial availability without lifelong guarantees of access.

As some scholars argue, international human rights law in this field has not yet been sufficiently developed (Steiner et al. 2008). Only a progressive implementation of these concepts at the national level and their inclusion in domestic legal frameworks could suggest their consolidation in the States concerned. It is positive that some developing countries, such as Brazil, Kenya and South Africa, adopted domestic rules clearly prohibiting double standards and placebo trials relying on existing guidelines.[32]

[32] In Brazil, the National Health Council issued a Resolution (No. 251/1997) which expressly refers to post-trial obligations. The research sponsor or other specified groups have a legal duty to provide post-trial treatment at least to research participants in clinical trials carried out in Brazil. In Kenya, there are the 2004 National Council for Science and Technology (NCST) "Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya" ("human subjects guidelines") and the 2005 Ministry of Health (MoH) "Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines" ("vaccines guidelines"), and in South Africa, the Department of Health (DoH) "Ethics in Health Research: Principles, Structures and Processes", which was drawn up by members of both the Department and the Interim National Health Research Ethics Committee, appointed under the National Health Act of 2003.

At the regional level, with particular reference to the EU and to the COE, effective protection of research participants in developing countries has already been foreseen. The EU has adopted several directives that clearly prohibit double standards and the use of placebo. Due to their legal value, they have been implemented at national level. Furthermore, the European Medicine Agency (EMEA), through its advisory activity to the European Commission, plays an important role in protecting and promoting patients' rights (Schipper and Weizig 2008).

Only a recognition of the link between fundamental human rights and research ethics issues in developing countries, and the enforcement of human rights of vulnerable populations in international treaties and in national legislations can provide adequate safeguards to research participants. Medical experimentation continues to be a critical step in improving human health, but must come under strict limitations and control in accordance with the Kantian imperative (in his "Metaphysical Foundations of Morals") to "act so as to treat man… always also as an end, never merely as a means".

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Chapter 8
Research Involving Human Subjects and Human Biological Material from a European Patent Law Perspective. Autonomy, Commodification, Patentability

Tomasz Zimny

8.1 Introduction

The fact that human medical research plays a central role in the development of contemporary medicine is quite understandable and does not require extensive explanations. Also, it is quite obvious that it is only a part of a lengthy and costly process resulting in the marketing of a new medicine or medical product or, in quite the opposite way, the termination of the project. Hence, the conclusion that medical research leading to the development of new kinds of medicine is both costly and risky from an economic point of view.

It will also not be surprising that an area of human activity, such as that of medical research, in which there are large investments and high financial risks on the one hand, and personal, existential risks on the other, is predisposed to be an area where tensions, conflicts or atrocities are, if not inevitable, then at least likely. Examples of grave misconducts from the past, some of which are analysed in other parts of this book,[1] led to the adoption of various kinds of documents, also at international level, with the aim of providing guarantees that such types of misconduct will not happen again or will, at least, have limited range.[2] It is not the goal of this chapter to analyse those documents, but it may be worth mentioning some of them, such as the Nuremberg Code, the Belmont Report, various versions of the Declaration of Helsinki or the Convention on Human Rights and Biomedicine.

As has already been mentioned, investing in medical research may prove to be both costly and risky. One of the ways of providing those investing in this risky

[1] See further Fiona McClenaghan's Chap. 2 and also Rael Strous's Chap. 3 in this volume.
[2] See further Ilja Pavone's Chap. 7 in this volume.

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endeavour with a prospect of revenue is to allow them to patent some of the results of their investments and hence give them a monopoly, for a limited period of time, with regard to the patented invention. Since the late-1800s, an ongoing process of harmonisation of patent law on a regional or global scale has been seen. The more prominent and recent legal instruments encompass such documents as the Convention on the Grant of European Patents (EPC), the Agreement on Trade Related Aspects of Intellectual Property (TRIPS) and the Directive on the legal protection of biotechnological inventions (Directive 98/44). The latter document was adopted within the EU in order to harmonise patent law with regard to biotechnological inventions. Its main provisions were incorporated into the Implementing Regulations of the EPC (rules 26–34). Hence, they are of significance to all EPC parties (currently 38). The Directive 98/44, allows for the patenting of inventions even if they concern a

> […] product consisting of or containing biological material or a process by means of which biological material is produced, processed or used. Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature. [art. 3.1 and 2]

This also means that it is possible to patent biological material of human origin, albeit under some additional conditions, e.g. the isolation from the human body and indication of a function of the patented DNA sequence (see Bostyn 2003).

The rules aimed at ensuring ethically sound medical research on humans and those adopted in order to harmonise patent law have a common ground. In particular, rules referring to morality were introduced into patent law on biotechnological inventions, sometimes even excluding the patentability of some of them.

Although some people question the morality of patenting biological material (e.g. DNA sequences) itself (Papaioannou 2008), the aim of this chapter is not to discuss the morality of patenting. Its aim is to look closer at those areas where the rules on human medical research and patent law intersect and influence the patentability of some inventions. Are contemporary rules of patent law, whose role is to ensure ethical research, efficient?

8.2 The Concept of Morality

What morality and moral behaviour are has been a "hot topic" for philosophers for thousands of years. Also, the problem of what "moral behaviour" of a physician and, more recently, of a researcher means, has been subject to a vivid discussion. The aforementioned attempts at ensuring ethically sound human medical research resulted in the adoption of various international guidelines introducing standards of research. They name some features of research, which, even if not sufficient, can at least be treated as necessary conditions of ethical research. For the purposes of this chapter, one can mention, for example, the Belmont Report (adopted in 1979 by The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research), principles of respect for persons, beneficence and justice or, in a more detailed way, the seven principles proposed by Emanuel et al. (2000): valuable scientific question, valid scientific methodology, fair subject

selection, favourable risk-benefit evaluation, independent review, informed consent, and respect for enrolled subjects.

The concept of morality is also present in the European patent law. The issue of what is understood by this concept and how it should be applied is, however, quite complicated. The EPC forbids the granting of a patent for an invention, should its commercial exploitation be contrary to "ordre public" or "morality" (EPC, art. 53a). This same exception to patentability was introduced into the Directive 98/44, along with examples of such inventions. The first problem is that various language versions of those acts use a variety of terms to refer to those criteria for patentability: While the English version, for example, uses the term "morality", the German one uses the term "gute Sitten", which would literally translate into English as "good customs". These differences have been a source of controversies, as the three language versions of the EPC are equally authentic (EPC, art. 177(1)), however, for the purposes of the examination of inventions, the terms should rather be treated as equivalent—otherwise the patentability of an invention would depend on the language of the patent application (see also EPO No. 315/03, pt. 11.7).

Another problem, probably more important from the point of view of this chapter, is the actual content of the term "morality" used in patent law. The Technical Board of Appeals of the EPO[3] made an attempt to define this term and decide about the normative basis of the examination of inventions from the point of view of morality:

> The concept of morality is related to the belief that some behaviour is right and acceptable whereas other behaviour is wrong, this belief being founded on the totality of the accepted norms which are deeply rooted in a particular culture. For the purposes of the EPC, the culture in question is the culture inherent in European society and civilisation. (···) inventions the exploitation of which is not in conformity with the conventionally-accepted standards of conduct pertaining to this culture are to be excluded from patentability as being contrary to morality. [EPO No. 356/93, pt. 6]

Invoking "conventionally-accepted standards of conduct pertaining to [European] culture" as a standard of examination is quite problematic given the fact that among EPO members, there are countries of quite different cultural backgrounds, such as Poland, the United Kingdom, Albania, or Turkey. Those countries also have quite different rules regarding issues which are subject to heated moral debate, such as the admissibility of embryonic stem cell research (see, above all, Isasi and Knoppers 2006). Consequently, the patent examiner, when facing an invention they consider morally disputable, has to refer to quite a vague set of principles, probably depending on their nationality, cultural background and other variable factors, thus making the process of patent granting uncertain in this respect (see also Warren-Jones 2007). A question thus arises, whether the patent offices should actually be guardians of morality (Du Vall 2008, p. 380).

Another problem occurs in the case of human medical research. Namely, how does the definition of morality cited above fit within the framework of principles

[3] European Patent Office—an office whose main competence is granting patents according to the EPC.

constituting ethically sound research. It would be quite easy to assume that principles allowing for human medical research only in case of a favourable risk-benefit ratio, fair subject selection, obtaining informed consent, etc. are simply part of "conventionally-accepted standards of conduct pertaining to [European] culture". We should not jump too quickly to conclusions though, as the matters are a bit more complicated.

8.3 When is an Invention Immoral?

Human medical research is, at least in the case of the law of many European countries, a strongly regulated area of human activity. The aim of many of those legal acts is to protect very important values, such as human autonomy, human health, life, scientific validity of research, and human dignity. Their aim then, is to ensure that human medical research is carried out in a moral manner. Those rules apply to the process of obtaining and later testing medicines or medical products. Hence, they often apply to activities which only precede or lead to obtaining an invention (see also Hoedemaekers 2001). The question which arises then is, whether the exception to patentability discussed ("immoral invention") applies to inventions whose exploitation per se is not contrary to morality, but which were obtained in an immoral way. Does the EPC allow the patenting of a medicine, for example, which was created in a developing country with violation of the informed consent requirement or the risk-benefit ratio principle?

An analysis of existing literature and rulings does not lead to a definite conclusion. In the decision G 2/06, for instance, the Enlarged Board of Appeals of the EPO decided that an invention whose obtaining, at the date of the filling of the application, required the destruction of embryos, should be considered contrary to morality, even if later technological developments rendered such destruction unnecessary. By analogy, if a drug was obtained with the violation of some basic principles of ethical research, it should not matter that it is, in fact, possible to obtain such a product in accordance to those principles. An opposite conclusion to the one mentioned would lead to rewarding applicants with patents for immoral activities (see also Moufang 1994).

On the other hand, other authors point out that although this line of argumentation might be valid, the way Article 53(a) of the EPC is constructed now does not provide a basis for a definite support of such a position (Żakowska-Henzler 2006).[4] This, together with a general rule that exceptions to patentability should be interpreted

[4] The "fruits of the poisonous tree" approach towards patentability of certain inventions has recently been strengthened by the opinion of Attorney General Yves Bot, before the EU Court of Justice and the judgement of the Court in the case C-34/10. In the opinion, we read *inter alia* that "An invention must be excluded from patentability where the application of the technical process for which the patent is filed necessitates the prior destruction of human embryos or their use as base material, even if the description of that process does not contain any reference to the use of human embryos." On the other hand, such approach has already been criticised by the doctrine as going too far (see, for example, Grund and Farmer 2011).

narrowly, may lead to a conclusion that the law does not forbid the patenting of an invention obtained in an immoral way. Furthermore, the assumption that one should not benefit from past wrongdoings is not as obvious and clear as it seems (see, for example, Takala and Häyry 2007), while patenting itself is sometimes considered a bargain between the state and the inventor, where the inventor is rewarded not for obtaining the invention, but for revealing it (Crespi 2000).

Hence, even if the assumption that the principles of ethical research mentioned above somehow constitute a part of the set or system of moral norms defined by the EPO, it might not matter. It is not clear whether unethical research leading to the obtaining of an invention can be a reason for not granting a patent.

The question of autonomy, so vital from the point of view of human medical research, was also taken under consideration by drafters of the EU Directive 98/44. According to recital 26:

> If an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law.

In other words, a person whose DNA is used to obtain a patented invention should have an opportunity to agree to patenting. The recital quoted was not transferred into implementing regulations of the EPC, however. Its binding force is still disputable and, furthermore, even if it were binding, it would apply only in EU member states and would probably require implementation into the national laws of the said states.

It would also be quite difficult to apply this rule in practice. It is not always easy to predict the use of obtained samples of biological material and whether they will serve to obtain patentable inventions. It is possible to a priori limit the scope of possible applications by enabling donors to exclude, for example, military applications in the consent form, however, in the case of patenting, such an opportunity may lead to "checking" the respective box in the consent form by default (which would then actually turn this consent into a sheer formality) or, in case of refusal, render the whole sample useless, as it may prove to be very difficult in future to track, which of the samples examined served to obtain an invention and which did not. The results of failing to do so could be quite undesirable. The whole invention would be considered unpatentable because of some sample being used earlier in the studies without a consent to patenting.

8.4 Examples of Immoral Inventions and How They are Defined

According to Article 5.1 of Directive 98/44:

> The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

The aim of the cited provision seems to be the prevention of commodification of the human body and, furthermore, avoiding situations where elements of the human body which constitute parts of those bodies would be at this same time objects of somebody's exclusive rights.

However, according to pt. 2 of this same article:

> An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

The reasons for the introduction of that provision seem to be purely consequentialist—promotion of progress in the treatment of diseases (Directive 98/44, recital 17). A question now arises whether this provision does not in fact constitute a kind of backdoor allowance for some sort of commodification. The reason for this is that the law only requires one to isolate and identify a function of a fragment of the human body in order to treat it as patentable subject matter. This raises controversies, as some authors oppose the very idea of patenting DNA sequences or larger items such as stem cell lines, claiming that turning them into commodities may for example, have some adverse consequences or be wrong per se (Knowles 1999; Resnik 2002; Hanson 1999). Other authors reject such arguments by saying that, in this case, we do not actually have anything to do with commodification. Also, commercialisation of those DNA sequences, which also exist in the human body, does not influence the lives of humans, because their own DNA cannot be patented (Bostyn 2003).

Article 6.2 of the Directive 98/44 mentions examples of inventions whose exploitation would be considered contrary to morality or "ordre public". The list includes:

(a) processes for cloning human beings;
(b) processes for modifying the germ line genetic identity of human beings;
(c) uses of human embryos for industrial or commercial purposes; and
(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

The first exclusion is highly problematic and for various reasons. Firstly, unlike the quoted Article 5.1 of the Directive 98/44, it does not say about a "human body", but about a "human being", a term whose definition has been the subject of unsettled disputes for years (see, for example, Holm 1998; Warren 1973; Green 2002). Additionally, European legislations are inconsistent on this issue (Isasi and Knoppers 2006). The definition of cloning provided by the legislator in recital 41 of the directive is not very helpful in that matter either:

> any process, including techniques of embryo splitting, designed to create a human being with the same nuclear genetic information as another living or deceased human being

as it uses the term "human being" without defining it. Consequently, it is unclear whether the patenting ban applies only to reproductive cloning, or if it also

encompasses therapeutic cloning. Moreover, it should be noted that according to Article 5.1 of the directive, only a process could be patented, because the human body, at any stage of its development, cannot be patented. Furthermore, the patenting ban only limits possible sources of financing of such activities as human cloning, but does not forbid it at all (Bostyn 2003).

This same situation applies to the second of the mentioned exceptions; the one referring to the modification of germ line genetic identity of human beings. On one hand, this type of activity is very often associated with the designing of the genetic make-up of children, which is supposed to violate their dignity (Häyry and Häyry 1997), or various kinds of "slippery slope" arguments associated with this kind of modification (Fukuyama 2002). On the other hand, hopes are associated with this type of genetic therapy. In particular, hopes for the prevention of genetic diseases, such as Huntington's disorder (Häyry and Häyry 1997). The introduction of this kind of exclusion results in limitation of possible sources of financing for research into this kind of technology, while not forbidding it definitely.

Problems of a similar nature are connected with the third exception mentioned—the uses of human embryos for industrial or commercial purposes. *Prima facie*, the goal of this exception is to prevent the commodification of the human body at very early stages of its development. In this respect, the rule mentioned is supposed to be complementary to the provisions set forth in Article 5.1 of Directive 98/44. However, the introduction of this rule has some confusing results. The case law of the European Patent Office excludes the patentability of stem cell lines if their obtaining required the destruction of human embryos[5] [EPO No. G 2/06]. Consequently, the European patent law treats research on embryonic stem cells as morally wrong, while at the same time, such research is allowed in most European countries and can be financed from public funds (e.g. the 7th EU Framework Programme). Furthermore, in some European countries, it is even allowed to create embryos for research purposes (Isasi and Knoppers 2006) or create human–animal hybrids for research purposes (see further HFEA 2007), which poses a problem in itself from the point of view of patent law (Rabin 2006). In this respect, European patent law is very conservative compared to most European legislation.

8.5 Conclusions

Although provisions referring to morality have been present within patent law for centuries, they have gained significance with the advent of so-called biotechnological inventions. Such provisions are also supposed to strongly influence human medical research and the commercialisation of its effects. Their aim, in this

[5] Such exclusion was recently mentioned also in an EU Tribunal judgment, in case C-34/10. This judgment could not be thoroughly commented in this paper due to the date, at which it was passed.

respect, is to contribute to the ethical conduct of that research, and so they should be compatible with other laws created for this same purpose. The way the provisions of patent law are constructed, their actual content and sometimes place within the system puts their effectiveness in question.

The restrictions placed within European patent law sometimes represent only one position on subjects, about which there is a lively moral dispute, far from being settled (for example, in the case of germ line genetic therapy). They are often formulated in a way which strongly hampers the possibility of their application, which may have a negative effect on the certainty of law (for example, by using vague terms like "human being"). On the other hand, defining such terms would probably also not be desirable, because of the first reason given. Even if some of the restrictions mentioned are a representation of some particular moral positions, they do not ensure their protection. Furthermore, it is unclear what kinds of moral positions constitute a basis for some of the restrictions discussed in this chapter, and whether they are consistent with each other (vide the commodification of human biological material issue).

The very concept of morality used within European patent law is quite confusing, as it is defined by reference to criteria of unclear content (for example, conventionally-accepted standards of conduct pertaining to European culture). Even if we were to decide that principles of ethical human research are part of those standards of conduct, there are little, if any, mechanisms of their effective protection by means of patent law. This turns some of the provisions referring to morality to mere declarations instead of means for ensuring their effective execution.

Turning the contemporary patent law provisions into effective means of protection of values important in human medical research would require a thorough reform of the patent law system. Such reform would, however, require strong concessions on the part of many states as it would, for example, require actual definition of such terms as "human being" or "morality". The biggest problem posed by contemporary legislation may not be the fact that such sensitive matters are regulated; the problem seems to be the quality of that legislation, which results in a lack of certainty of law. For extended periods of time, the inventors (or investors) are not certain whether an invention into which they invest will be patentable or not. The application of patent law provisions, which usually takes place at the level of patent examiners, is being moved to some higher bodies and requires extensive interpretation. In the case of the previously cited decision G 2/06, for example, it took about 12 years to answer the question about the patentability of certain stem cell lines. By the time the decision was passed, rules forbidding patenting of certain biotechnological inventions had already been in force for ten years. Of course, there are some procedural reasons for this kind of elongation, yet the uncertainty of law contributed to it as well. If the patent examiners are to apply norms of morality, at least a reference as to what kind of norms they should be, ought to be included within the EPC or state law.

Another option would be to actually drop the subject of morality protection within the patent law. The idea is not as surprising as it initially seems. The patent

itself does not grant a right to utilise an invention. Rather, it only allows for the prevention of other subjects from utilising it. Furthermore, issues connected with human medical research are and should be regulated by different branches of law: in acts regulating clinical trials, medical research in general, the profession of physician, or even requirements set by publishing houses. This same applies to some other branches of research, such as stem cell research. Patent law provisions referring to morality do not prevent certain types of activities, rather, they potentially limit available sources of research funds. Should a type of research be considered immoral, it should be directly prohibited, not merely addressed by norms of patent law. In addition, the certainty of law suffers from the current state of affairs, as the patent applicant is unsure about the moral beliefs of the examiner who will examine their invention, and who is usually an expert in science, not in ethics.

The provisions of patent law referring to morality can also be treated (in face of their limited applicability) as moral declarations made by the European lawmaker. As such, however, they do not represent any common opinions and, furthermore, should be consistent with each other, which, as has been shown, is doubtful.

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Chapter 9
The Development and Validation of a Guide for Peruvian Research Ethics Committees to Assist in the Review of Ethical-Scientific Aspects of Clinical Trials

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9.1 Introduction

Peru, with a population of 28,220,764 reported in the 2007 census, is a young, the median age of population was 25-years-old, and multi-ethnic country. It is predominantly (72%) urban (Peru INEI 2007). Although the numbers of citizens considered poor or severely poor remain high at 44.5 and 15.1%, respectively (Peru INEI 2005–2007), poverty has declined. In addition, Peru has a weak educational base with high functional illiteracy rates of 33.3%. The health-care system is unequal, variable and depends on socio-economic conditions; thus, only 42.3% of the population in 2007 had some form of health-care insurance with access to essential medicines (Peru INEI 2007).

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Well-designed and well-conducted clinical trials (CT) have been regarded as the gold standard in clinical research because they can evidence the efficacy and safety of new medical products and their therapeutic, prophylactic or diagnostic properties. Nevertheless, it is essential while conducting the trials to respect human dignity, to protect the rights to self-determination and welfare of trial participants, whether they are healthy or patient volunteers, and to ensure that their physical and mental well-being is sufficiently protected. This is acknowledged nationally (Peru, The President of the Republic 2006, 2007) and internationally (OHSR 1949; NCPHSB BR 1979; Council of Europe 1997; CIOMS 2002; UNESCO 2005; WMA 2008).

The RECs are pillars of the system to protect the rights of the human subject who participates in clinical research. The Peruvian RECs are multidisciplinary and include health professionals and community representatives (Peru. The President of the Republic 2006, 2007), and are responsible for ensuring that research involving human subjects is carried out with methodological rigor, in accordance with national laws and regulations governing this practice, and adhere to a broadly accepted international ethics code: the Declaration of Helsinki and its amendments (Peru. The Congress of the Republic 1997, Article 28).

The RECs have accountability in the public health field to the society in which they are embedded, giving them "ethical and social responsibility" (Emanuel et al. 2000, 2004; Cortina and Conill 2005; Dixon-Woods and Ashcroft 2008). Essentially, they act through moral deliberation, assessing the potential risks that affect the rights and protection of the research subject and the possible social or scientific benefit (Emanuel et al. 2000, 2004; Dixon-Woods and Ashcroft 2008) by ensuring that research subjects are not merely used but are treated with respect and protection while they contribute to the social good (Emanuel et al. 2000).

The increased outsourcing of clinical trials to low- and middle-income countries that has occurred during the last 20 years is of growing interest (Hawkins and Emanuel 2008; Fisher 2009; Petryna 2009; Glickman et al. 2009; Olave-Quispe 2012; Homedes and Ugalde 2012). The CT laws and regulations in Latin America, and more specifically in Peru, are relatively new (Peru. The President of the Republic 2006, 2007). The first CT was authorized by the Ministry of Health in 1995, and the number of studies increased progressively until 2008 when a total of 825 CTs had been approved by the Peruvian NIH (National Institute of Health 2009).

Although Peru has made great strides in CT regulation in recent years, it still did not have a CT reviewing guide which could be used by RECs by 2008. Indeed, between March and July 2009, REC inspections by the Peruvian (NIH 2009) indicated that there were serious deficiencies in their ability to perform their moral functions, mainly because it appeared that the ethical-scientific reviews had become a mere administrative formality: 45% of the clinical research was reviewed by four non-institutional RECs[1] and in a short time, from 4 to 21 days.

[1] Profit-making RECs exist in Latin America that have been established to facilitate the approval of clinical trials in centre founded directly or indirectly by the pharmaceutical industry.

Furthermore, the idea of developing this guide was reinforced in the First Meeting of the Latin American Network on Clinical Trials and Ethics in Argentina (RELEM 2008), where it was found that other countries in the region had this kind of resource.

One topic that has generated ethical discussions about human experimentation in Peru concerns the "unfair social conditions" that make CT participation attractive for researchers and research subjects: People do not have access to medicines; people do not understand the risk of clinical research; a paternalistic model is widespread in the patient-physician relationship; there are weak regulatory agencies; and there are widespread conflicts of interest (including financial incentives to researchers to encourage recruitment). We speculate that these incentives are contributing to the violation of ethical codes governing human experimentation. We are concerned because the "social inequity" prevalent in the low- and middle-income countries, including Peru, and the limited "social responsibility" of our governments and local researchers can lead to the "exploitation"[2] of the most vulnerable groups (Hawkins and Emanuel 2008; Fisher 2009; Petryna 2009; Glickman et al. 2009; Lorenzo et al. 2010; Homedes and Ugalde 2012). That is why in our Guide, we prioritized doing an analysis of the "vulnerability" of the research subjects, since, according to international guidelines on ethics in human research (WMA 2008; UNESCO 2005; CIOMS 2002), and special care must be exercised when including this population in clinical research.

9.2 Objectives

The main objective of this project was to develop and validate an institutional guide to assist the Peruvian RECs in the revision of the ethical-scientific aspects of clinical trials. A secondary aim was to identify and analyse the ethical-scientific issues that arise in the RECs' review reports.

9.3 Methods

I. Review-synthesis of relevant bibliography on the ethics of research with human subjects and analysis of their applicability in the local Peruvian context.
II. Development and validation of the format and content of a guide for reviewing the ethical and scientific aspects of the clinical trials to be used for the Peruvian RECs.

[2] As Alan Wertheimer suggests, a fully voluntary transaction between A and B is exploitative if the division of the benefits and burdens created though the transaction is distributively unfair. In developing countries' research, the worries about the standard of care, the quality of informed consent procedures and the post-trial availability of interventions that have proved to be useful, all relate to exploitation (Hawkins and Emanuel 2008).

III. Identification and analysis of the ethical and scientific issues identified by RECs during CT reviews that were included in the RECs' decision reports.

9.4 Results

9.4.1 Review-Synthesis of Relevant Bibliography on the Ethics of Research with Human Subjects and Analysis of Their Applicability in the Local Peruvian Context

Many ethical codes and documents have been written during the past 50 years in response to ethical violations and to avoid future scandals in medical research involving human subjects, some of which are analysed by McClenaghan and Strous in this book (see Chaps. 2 and 3, respectively). During this period, the REC was established by a recommendation of the Declaration of Helsinki in 1964, and the fundamental ethical principles of justice, autonomy and beneficence were developed by the Belmont Report in 1978. In this way, there is agreement that:

> In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests. (WMA 2008)

Most recently, ethical reflection on research has occurred around the amended editions of the Declaration of Helsinki (Homedes and Ugalde 2009). The version of 2008 has led to several controversies due to its frequent changes and to the ambiguity of conflict areas in clinical research, areas of particular interest for low- and middle-income countries, such as: the use of placebo, the standard of care and the reasonable availability of intervention that has proven to be useful at the end of clinical trials (Emanuel et al. 2004; Hawkins and Emanuel 2008; Lorenzo et al. 2010). These key issues are analysed in detail by Comoretto and Pavone in this book (see Chaps. 6 and 7, respectively).

On the other hand, Good Clinical Practice (GCP) (ICH 1996) was adopted to encourage harmonization of the regulatory standard in clinical trials in the United States, the European Union and Japan. It promotes predominantly the quality of research and does not sufficiently emphasise the need to respect adherence to essential ethical principles. Currently, in the context of the globalization of CTs, most legislation in Latin America includes compliance with GCP (PAHO 2005) and the respect for the fundamental ethical codes, such as the Declaration of Helsinki (WMA 2008), CIOMS (2002) and the Universal Declaration of Bioethics and Human Right (UNESCO 2005) (see Table 9.1). However, this could change, since the FDA no longer requires that research that will be used in market

Table 9.1 The selected codes/guidelines of ethical safeguards in clinical trials at international level and local regulation reviewed included

Guidelines	Source	Year
	Fundamental	
Nuremberg code	Nuremberg Military Tribunal	1947
Belmont report	National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research	1979
International Ethical Guidelines for Biomedical Research Involving Human Subjects	Council for International Organizations of Medical Sciences in Collaboration with the World Health Organization	2002
Universal Declaration on Bioethics and Human Rights	United Nations Educational, Scientific and Cultural Organization	2005
Declaration of Helsinki	World Medical Association	1964
	Other	
Good Clinical Practice	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use	1996
Good Clinical Practice Document of the Americas	Pan-American Health Organization	2005
Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine	Council of Europe	1997
The Buenos Aires Declaration on the Ethics of Clinical Trials	Latin American Network on Clinical Trials and Ethics	2008
Guide for reviewing Clinical Trials protocols	Regional Research Ethics Committee Madrid, Spain	2007
Reviewing Clinical Trials: A Guide for the Ethics Committee	The University of Hong Kong Clinical Trials Centre, Hong Kong SAR, PR China	2010

(continued)

Table 9.1 (continued)

Guidelines	Source	Year
International Compilation of Human Research Protections	The Office for Human Research Protections and U.S. Department of Health and Human Services	2010
	Peruvian regulation	
Regulation of clinical trials	Peru. The President of the Republic	"D.S. N°017-2006-SA"
The amendment of the regulation of clinical trials	Peru. The President of the Republic	"D.S. N°006-2007-SA"
National Health Law	Peru. Congress of the Republic	"Ley N° 26842- 1997"
Law that outlines the rights of the users of the health system	Peru. Congress of the Republic	"Ley N° 29414 -2009"
Check list for reviewing clinical trials protocols	Research Ethics Committee, "Hipolito Unanue" National Hospital, Lima, Peru	2009

applications conducted on foreign soil adheres to the Declaration of Helsinki (Department of Health and Human Services FDA 2008). It is also important to mention that due to the poor ethical sensibility of the main stakeholders in the implementation of clinical trials, there are reports of CTs carried out in the Latin American region in violation of national laws and internationally accepted ethical principles (Fisher 2009; Petryna 2009). Moreover, while ethical problems during clinical trials are present in all parts of the world, they appear to be more serious in developing countries.

These concerns have highlighted the importance of developing guides for reviewing CTs, taking into account the cultural, social and economic needs of the developing countries and the respect for the International Human Rights Covenants, such as human dignity, solidarity, freedom of research, respect for privacy, confidentiality, non-discrimination, informed consent, integrity of research, intellectual honesty, and global health, as a gold standard for the performance of the RECs. Similarly, human rights are deeply argued for by Pavone and Zimny in this book (see Chaps. 7 and 8, respectively).

9.4.1.1 Timeline of Clinical Trials Regulation in Peru

The conduct of CTs in Peru until 2006 was governed by "the rule for use of drugs in clinical trials" approved in 1981 by the Ministry of Health (Peru. Ministry of Health 1981). In early 2004, it was decided to update the legislation because it had become obsolete. It did not address important specific aspects such as the responsibilities of those involved in the research, the scientific review of the protocols and new product investigation. Nor did it cover the regulation of Contract Research Organizations (CROs), RECs and research institutions and it did not include information on the need to conduct inspections. Revision was urgent, especially when taking into consideration the increased number of CTs that had been implemented in the country in recent years (Olave-Quispe 2010; Minaya et al. 2012).

By December 2004, in order to gain stakeholder commitment and collect information about the overall context of CT stakeholders, the Peruvian Office of Research and Technology Transfer ["Oficina General de Investigación y Transferencia Tecnológica" (OGITT)] of the NIH, which is responsible for CT approval, held a series of meetings with the Pharmacovigilance and Pharmacoepidemiology team of the General Directorate of Medicines and Devices (DIGEMID), which is the agency responsible for drug regulation. As a result, they issued the first draft regulation of Clinical Trials for the country. This draft was approved by "DS N° 017-2006-SA" (Peru. The President of the Republic 2006). However, entry into force of the new regulation coincided with a change of government. The new Minister of Health, a well-known clinical researcher in oncology, who was only in office from July 2006 to November 2007, decided to revise the new regulation without evidence proving that it was faulty. The regulation was amended by "DS N° 006-2007-SA" (Peru. The President of the Republic 2007). The amended document weakens the protection of research subjects, as reported below (see Fig. 9.1).

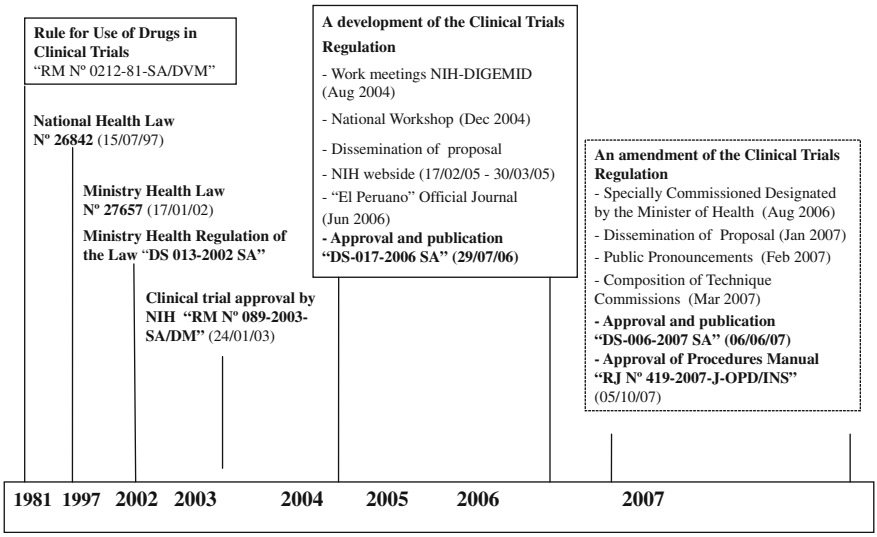

Fig. 9.1 Timeline of the clinical trials regulation in Peru and institutions

9.4.1.2 Most Important Changes in Clinical Trial Regulations in Peru, 2007

The main changes introduced by the amendment of the CTs regulation were described and criticized in detail by Minaya et al. (2012), Olave-Quispe (2010) and in an expert meeting on clinical trials and protection of research subjects in low-income and developing countries (Olave-Quispe 2007).

The approved changes would have the main following impacts:

- The sponsor of a CT will no longer have to purchase an insurance policy covering the research subjects for all CT conducted in Peru. Currently, they could have to declare that patients will have access to free treatment and compensation for any harm that they may suffer. In particular, if the CT is sponsored by the university or the national or international institute of health.
- It will no longer be necessary to specify the obligations of the research sponsor, the research institution and the principle investigator in a contract.
- All the responsibility lies with the sponsor of the research; the principal investigators and the institutions in which research is conducted are exempt from any responsibilities.
- The regulatory agency will have only 40 days to approve the clinical trials and only 7 days to approve the importation of the research drugs.
- There are changes in the constitution of the REC.
  - The minimum number of REC members is reduced from seven to five and only one member should have attended a course in Bioethics.

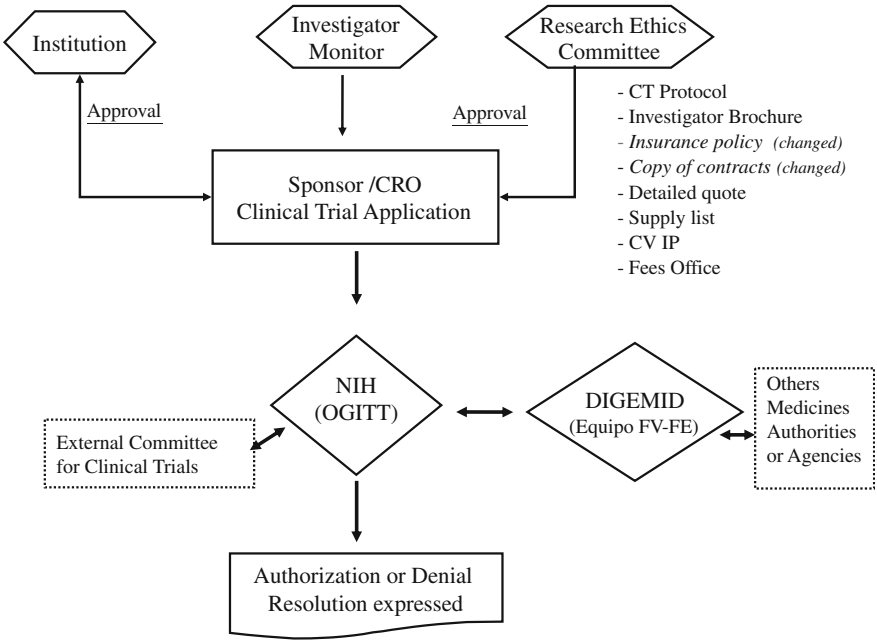

Fig. 9.2 Clinical trial application approvals

- It allows the creation of private non-institutional RECs, without appropriate geographic and institutional limitations.
- As a result, the evaluation of the CTs is focused on a few non-institutional RECs, so-called "independent RECs", and the changes permit "REC shopping behaviour" (Peru. NIH 2009).

9.4.1.3 Clinical Trial Application Approval

Each CT application submitted to the NIH is a two-step process that requires the coordination of two public entities (see Fig. 9.2):

1. An assessment of the safety of the investigational product that is carried out by the General Directorate of Medicines and Devices (DIGEMID).
2. The suitability of the protocol from the scientific or methodological, ethical and legal perspectives, which is performed by the Office of Research and Technology Transfer (OGITT) of the Peruvian NIH. The NIH has an external Technical Committee for Clinical Trials and can request a second opinion from researchers/entities not linked to the external technical committee, especially if there are discrepancies during the evaluation process. This opinion must be

based on best practices and the feasibility of CTs, according to international ethical principles and internal institutional procedures (Fig. 9.2).

9.4.2 Development and Validation of the Format and Content of a Guide for Reviewing the Ethical-Scientific Aspects of the Clinical Trials to be Used for the Peruvian RECs

9.4.2.1 The Development of the Content of the First Draft Guide

We constructed an ethical-scientific Review Guide by carrying out a cross-cultural adaptation of a guide for reviewing clinical trial protocols developed by the Regional Research Ethics Committee of Madrid (Asensio et al. 2007) in the Peruvian REC context. We selected this guide because it included the parameters we wanted to include, based on our review of the above-mentioned documents and because the lead author (SOQ) was very familiar with it after having completed her visiting research in Madrid. The legal aspects were modified taking into account the Peruvian legislation (Table 9.1, Fig. 9.1).

9.4.2.2 The Validation of the Format and Content of the Guide

The contextualization of the "first draft Guide" to the research conditions in Peru was carried out in collaboration with the members of the REC linked to the Peruvian NIH, who agreed to participate. We received written comments on the wording of the questions and on the validation method, including changes to scales we had planned to use in the subsequent meetings with selected RECs to validate the Guide.

The "second draft Guide" was reviewed in collaboration with local experts, reviewers of clinical trials at the OGITT-NIH and international experts on ethics and clinical research, including: (1) The coordinator of the Latin American Network on Ethics and Clinical Trials (RELEM), (2) the ex-Executive Secretary of the National Commission of Ethics and Research in Brazil, and (3) the Executive Secretary of the Regional Ethics Committee in Clinical Research in Madrid. Most of this work was executed through e-mail exchanges.

The "second draft Guide" was then contextualized to the situation in Peru with the assistance of a selected sample of 27 RECs registered by the NIH. Fourteen RECs were selected according to pre-determined criteria (RECs with the highest percentage of studies assessed/total studies assessed by all RECs, and/or that had at least one member trained in bioethics) were invited. Twelve RECs with a total of eighty members agreed to take part in the "discussion groups" and 13 RECs agreed to "send the review reports". Since we had a limited budget, we had to exclude all RECs operating outside the Peruvian capital, Lima. Of the 13 RECs

that were excluded, five were located outside Lima, and eight in Lima but they had not yet started their activities or they had only assessed a handful of studies.

9.4.2.3 Process in the Discussion Group

1. We identified the "clinical trial cases" which represented the four most common medical conditions that are targeted by current research (diabetes mellitus, breast cancer, HIV, and paediatrics), and engendered a controversial deliberation which had been rejected in the past two years by the OGITT-NIH. The dossier of the clinical trials cases that we gave the RECs to review contained a summary of the CT protocol and their respective informed consent.
2. We had a short meeting with the chair of every Peruvian REC outlining the importance of the guide and its development process. We also sent an official letter from the NIH, and the study protocol (including a summary of our project, the informed consent and the clinical trial case that they had been assigned to review).
3. After all the members of the selected RECs had accepted their participation in the study, they reviewed the clinical trial cases following their regular deliberation procedure, and sent us the first review reports.
4. After we had received the first review reports, we sent the "second draft Guide" we had developed and scheduled the date when we would hold a discussion group with all the members of the RECs to explain the guide.
5. Four Peruvian NIH professionals with experience in the ethical, legal and methodological review of CTs visited each of the 12 RECs and explained each of the items in the Guide. These meetings took place from 2 November 2009 to 18 December 2009.
6. After the discussion groups, the members of the RECs reviewed the clinical trial cases they had been assigned for a second time using second draft Guide criteria and sent us a second review report of the CT cases. These second reviews were received between 20 December 2009 and 15 June 2010 (see Fig. 9.3).

9.4.2.4 The Information Analysis and the Content of the Final Version of the Guide

The Guide was edited in the Spanish language in August 2010 and it has been available at http://www.ins.gob.pe/insvirtual/hcnsopde.aspx?87 (Olave-Quispe et al. 2010). We emphasised in the introduction that all clinical research involves risks and the probability that they may cause serious physical or mental harm depends on the characteristics of each research project. To assess whether a project is considered "ethical" and respects the rights of research subjects, the first thing is to ensure that the research question is relevant and the research methods are rigorous. Once these two conditions have been established, the REC has to ensure

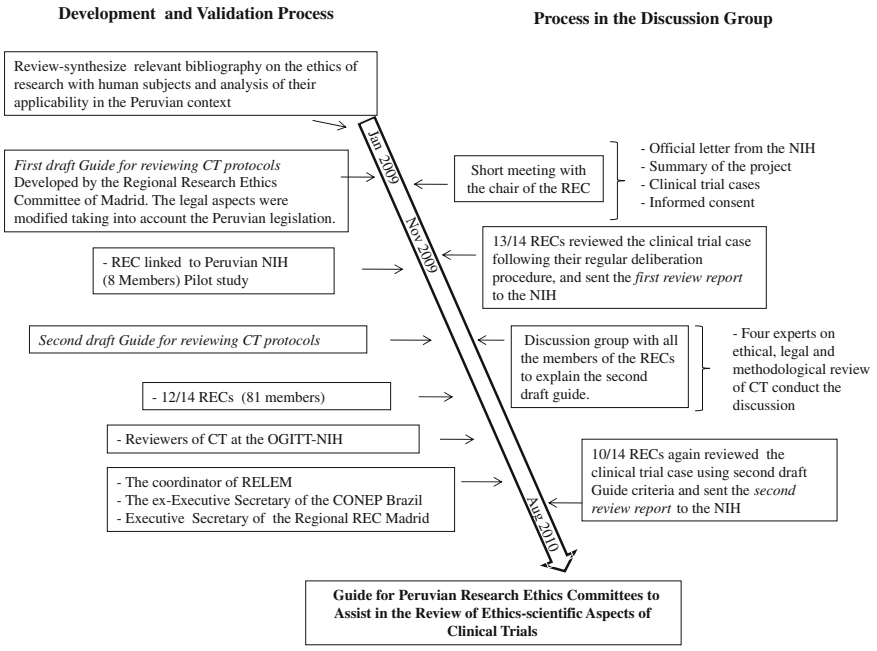

Fig. 9.3 Development and validation of a guide for reviewing the ethical-scientific aspects of clinical trials

that the following principles will be honoured during the trial implementation: (1) Autonomy (informed consent suitable and freedom to leave the study without any negative consequences for the patient), (2) justice (distribution of risks across different population groups, including social strata), and (3) beneficence and nonmaleficence (the balance of risk and benefit favourable for the research subject; predictable risk versus expected benefits) (OHSR1949; NCPHSB BR 1979; Council of Europe 1997; CIOMS 2002; Ashcroft 2003; UNESCO 2005; Galende 2008; WMA 2008).

Moreover, RECs in developing countries should ensure that the proposed research is responsive to a health need in the community and that need falls within the health research priorities of the Peruvians (CIOMS 2002); thus, they should restrict research using expensive drugs and with reduced value in terms of efficacy and safety than existing drugs.

The review of the respect for justice became important in the Peruvian context because it means that the benefits and burdens of research should be supported and distributed "equally" in society, which required ensuring representation of all socio-economic and cultural groups, unless precluded by the characteristics of the trial. The recruitment of people among the lower socio-economic classes who would otherwise have been unable to access treatment, and who, therefore, should be considered "vulnerable" was especially worrying.

9.4.2.5 Other Selected Items Added to the Content of the First and Second Draft Guide

The other selected items added to both versions of the Guide are the following:

- A review of the social value for Peru of the research to be conducted, including the benefits to those involved in the implementation of the trial, such as the dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements. An enhancement of the assessment of the justification for the use of placebo and identification of the situations in which it was ethically inappropriate.
- An emphasis on the importance of ensuring that clinical trial participants would continue to have access to the experimental treatment if is determined that they can benefit from it.
- RECs should also assess the competence and experience of the principal investigator to conduct the trial, and the appropriateness of the timeframe. They should also assess the adequacy of the local health-care and physical infrastructure.

Additional items were added to review the process of obtaining informed consent and verifying that it is understood. An effort was made to highlight the following:

- The possibility for the participant to consult with others (family, doctor) before making the decision to participate in the trials.
- Ensure that the patient understood the freedom to refuse or withdraw his/her participation in the study at any time and without penalty or fear of retribution.
- Provide enrolled participants with information that arises in the course of the research study.
- Inform participants and the study community of the results of the research.
- The need for an additional informed consent when the clinical trial called for the use and the conservation of human genetic data, human proteomic data and biological samples.

9.4.3 Identification and Analysis of the Ethical-Scientific Issues which Surfaced During CT Reviews by RECs that were Included in the RECs Decision Reports

We used "content analysis"[3] (Hsieh and Shannon 2005; Gray et al. 2007), a qualitative methodology that complemented the internal validity of the validating

[3] Content analysis is defined as a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns (Hsieh and Shannon 2005).

Table 9.2 Allocation of the clinical trial cases by medical conditions to every REC

Medical conditions	RECs (n)
One case of diabetes mellitus	Institutional RECs (7), Non-institutional REC (1)
One case of breast cancer	Institutional RECs (2)
One case of HIV	Non-institutional RECs (2)
One case of infant mycosis	Institutional REC (1)

process, to identify and analyse ethical and scientific issues in the RECs' review reports before and after applying the guide.

This methodology permits the extension of the theory of ethical-scientific issues explained in the Guide when it is being applied by the members of the RECs and permits the fostering of a clear understanding of the RECs' members.

In making their determination, an REC could reach three possible decisions:

- A "favourable" opinion means that a clinical trial is approved without further amendments;
- an "unfavourable" opinion means that a clinical trial is rejected; or
- a "provisional" opinion which requires a response to be made to the REC addressing issues observed.

The allocations of the clinical trial cases selected, according to specific medical condition criteria, to every REC are shown in Table 9.2.

In this part of our study, 23 review reports sent by 13 RECs were analysed. We considered: (1) the decision expressed in the review reports, and (2) the ethical-scientific issues mentioned in the review reports as indicators of quality.

Firstly, the decisions expressed in the review reports were classified, as shown in Table 9.3. The result underlines that only five RECs were in agreement with the Peruvian NIH in rejecting the CT case before applying the Guide, and favourable opinion increased in one REC after applying the Guide, which suggests that applying the Guide did not influence the decision of the RECs.

We subsequently analysed the 305 ethical-scientific issues (186 and 119, before and after applying the Guide, respectively) identified from the RECs' review reports. The classifications of the text data highlighted were carried out using the ethical-scientific issues of the Guide. We identified nine subcategories within the overall category of "ethical-scientific issues" to characterize the types of issues raised by the RECs. They are in congruence with the selected items added to the content of the first and second draft Guides and support the theory of the ethical-scientific issues (see Table 9.4).

In summary, we can observe an increase in the number and sometimes in the quality of ethical-scientific issues raised in the RECs' review reports after applying the Guide in the reviewing process, although there does not seem enough to improve the decisions expressed in the RECs' decision reports. It can be explained as an initial tangible effect of applying the Guide and by the

Table 9.3 Decisions expressed in the RECs' decision reports

Decision	Total reports (n)	Before applying guide (n)	After applying guide (n)
Favourable	3	1	2
Provisional	12	7[a]	5
Unfavourable	8	5[b]	3
Total reports	23	13	10

[a] 1 REC did not sent the 2nd review report (after applying our guide)
[b] 2 RECs did not sent the 2nd review report (after applying our guide)

Table 9.4 Types of ethical-scientific issues raised by the RECs

Ethical-scientific issues	Before applying guide		After applying guide		Total reports	
	n	%	n	%	n	%
Justification, objectives and principal outcome	11	9.2	19	10.2	30	9.8
Design issues, randomization and dummy of treatment	4	3.4	17	9.1	21	6.9
Selection criteria and vulnerable groups	12	10.0	16	8.6	28	9.2
Clinical equipoise, reviewing treatment and placebo use	17	14.3	30	16.1	47	15.4
Safety and quality of monitoring	29	24.4	36	19.4	65	21.3
Risk-minimization, adequacy of investigator and physical infrastructure	8	6.7	12	6.5	20	6.6
Informed consent procedures	24	20.2	39	21.0	63	20.7
Protecting confidentiality	7	5.9	5	2.7	12	3.9
Insurance policy and post-trial availability	7	5.9	12	6.4	19	6.2
Total reports	119	100.0	186	100.0	305	100.0

current performance level of the RECs. It highlights the engagement and the technical competence that all the members of RECs should have towards improving the quality for reviewing clinical research using ethical-scientific standards.

9.5 Conclusions

We need to take into account the historical, legal and social context of the stakeholders in the clinical trials, and we highlighted the amendment to the legislation of clinical trials in 2007 as a major setback in the social responsibility and transparency of Peruvian institutions, as we described in the summary in our study. These changes and the short time we had to complete our study imposed limits on how far it can be generalised to the current Peruvian context. However, this project resulted in a Guide for reviewing the ethical-scientific aspects of the clinical trials to be conducted in Peru and setting a standard for the performance of Peruvian RECs.

The guide was developed by a multinational collaboration taking into account the Peruvian context, so it will be useful for those who work in RECs and research institutions, or who are regulators or inspectors, researchers, research monitors, or anyone with responsibility for any aspect of clinical research that involves humans. We believe the development and evaluation method can be readily applied in other countries. The focus on the ethical principles of non-exploitation and ensuring the relevance of the research to the country in which the research takes place are of particular importance in developing countries.

The field work confirms that the guide served to deepen REC's discussion. Although, there seems not enough to improve the final decisions of the REC, in order to review the advisability of allowing or not the conduct of investigation.

As has been documented in other countries, the performance of REC to review the ethical and scientific aspects of clinical trials is limited and we need to find additional and alternatives strategies to protect the human subject involving in clinical research. However, the content and format of the Guide should encourage the development of critical skills and strong scientific and ethical reflection by RECs responsible for the approval and monitoring of clinical trials.

We hope that its dissemination and use will contribute towards ensuring respect for human rights, including human dignity and fundamental freedoms, and to protect public health.

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Part III
Conflicts in Medical Research

Chapter 10
Conflicts of Interest in Medical Research: What can Ethics Contribute?

Verena Sandow, Jan Schildmann and Jochen Vollmann

10.1 Introduction

The aim of this article is to analyse the concept of conflicts of interest in medicine and, more specifically, with respect to clinical research from an ethical perspective. The topic of conflicts of interest in medicine has received an increasing amount of attention in recent years. This is especially valid with respect to the role of the financial interests of physicians which might compromise the primary interests of medicine (for an overview, see Lo and Field 2009). To illustrate the issue at stake, one may refer to an example published by Anekwe on the topic of conflict of interest.

> […] pharmaceutical companies draft favourable scientific articles, send them to academic physicians or researchers who sign on as author, and publish the articles in medical journals. (Anekwe 2010)

Conflicts of interest in medicine spark off numerous conceptual and practical questions. How should we define conflicting interests and obligations in medicine? How can we recognise them and, last but not least, what are acceptable strategies to handle them? In recent years, a considerable amount of literature on the concept of conflicts of interest as defined from a medical perspective has been published (Brody 2011; Thompson 1993). In addition, there is also literature on practical issues, for example, on guidance regarding the disclosure of conflicts of interest in medicine (Campbell 2010; Klemperer 2008). However, to our knowledge, there is

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comparatively little literature from an ethical perspective which analyses the normative premises and implications of conflicts of interest in medicine.

This article focuses on the ethical aspects of conflicts of interest in medicine, and on the possible contribution of ethics with respect to clarifying the terms and meanings of conflicts of interest and related concepts. Initially, we will analyse the different definitions of conflicts of interest and distinguish those from other types of ethical conflicts in medicine. This will be followed by an ethical analysis of the role of ethical principles in the context of conflicts of obligation and conflicts of interest as major ethically relevant conflicts in context to clinical research. In the final part of our paper, we point out relevant challenges for the identification and management of conflicts of interest conceptually, as well as practically.

10.2 Conflicts of Interest: Definitions and Concepts

A widely used definition of conflicts of interest is given by Thompson:

> A conflict of interest is a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or validity of research) tends to be unduly influenced by a secondary interest (such as financial gain). (Thompson 1993)

According to this definition, patient welfare or the validity of research are two examples for primary interests of medicine in equal measure. These interests can be affected by secondary interests. While financial interests, as mentioned in the above definition, are in the focus of the current debate on conflicts of interest, it should be noted that there are also a number of other secondary interests, such as to promote one's career or prestige.

In his somewhat different definition of conflicts of interest, Morreim distinguishes between conflicting obligations and one's self-interest:

> In a conflict of interest, one's obligation to a particular person or group conflicts with one's self-interest. A physician, for example, is ordinarily obligated to provide his or her patients with only the care that is reasonable and medically necessary, even though the physician may earn more money through unnecessary interventions. (Morreim 1995)

In this definition, primary interests are translated as the obligation a physician has to follow, while secondary interests are coined as self-interests. We will discuss the limitations of such a translation in a later part of this article, but, for the moment, we will keep both definitions in mind and use them as a starting point to distinguish between two other ethical conflicts which are sometimes also coined as conflicts of interest—conflicts of obligation and conflicts of commitment.

According to the following explanation by Morreim, a conflict of obligation exists between primary goals in equal measures:

> Conflict of interest should be distinguished from conflict of obligation, in which one's obligation to one person or group conflict with one's obligation to some other person or group. The latter need not per se involve any threat to the agent's own interests. (Morreim 1995)

A standard example of a conflict of obligation in the context of clinical research is the conflict a physician researcher may face when making a decision which affects patient care, as well as the validity of a research project. We will come back to this problem later on, but at this stage it should be noted that, compared to the debate about conflicts of interest, there is already a significant amount of literature with respect to the ethical analysis and handling of conflicts of obligation in medicine (Vollmann 2000).

The second type of conflict which needs to be distinguished is that of a "conflict of commitment". In the publication of the Institute of Medicine already mentioned, Lo and Field define conflicts of commitment as follows:

> Conflicts of commitment often involve a conflict between what institutions view as employees' primary responsibilities to the institution and the employees' outside commitment. (Lo and Field 2009)

The focus of this conflict is on the fact that a person has an honest activity in his/her spare time, such as a voluntary fire fighter or some kind of honorary office. However, from the perspective of the employer, all the obligations the employee has in his/her free time are subordinated to the obligation at work. Similar to conflicts of obligation, conflicts of commitment deal with two respectable activities. However, in contrast to conflicts of obligation, the contract with an employer and the respective expectations regarding its fulfilment provide some framework for the concrete decision in practice (Lo and Field 2009).

In the following, we will focus on the ethical analysis of conflicts of interest and conflicts of obligation relevant to medical research. We will do so on the basis of mid-level ethical principles which will be specified to concrete conflicts. Our aim is to provide an ethical framework for the analysis. We also demonstrate the different roles of ethical principles, which differ with respect to conflicts of obligation on the one hand, and conflicts of interest on the other hand.

10.3 Conflicts of Obligation in Medical Research

Conflicts of obligation in medical research are one of the most prominent topics in biomedical ethical literature (Beauchamp and Childress 2009). A physician researcher may be confronted with such a conflict due to his/her double role in medicine. On the one hand, he/she has to attend to the patient's welfare. On the other hand, he/she is obliged to keep up standards of good scientific research. While in many cases it seems to be no problem to fulfil both obligations, there may be situations in which a physician wants to act in a certain way that he/she believes will promote the patient's health in the best possible way. However, by doing so, he/she runs the risk of violating the research protocol designed to get as good evidence as possible. The design of clinical research may take this double role into account and may try to minimize conflicts of obligation, for example, by separating the role of the physician interacting with patients from the role of the

researcher focusing on the data. However, in practice, this is not possible in all circumstances.

Numerous ethical theories and methods have been developed to find out if the conflict occurs between equally valued obligations and how to approach the ethical dilemma. One frequently mentioned approach to ethics in medical research and clinical practice is so-called principlism. Beauchamp and Childress (2009) formulated the four mid-level principles of autonomy, beneficence, nonmaleficence, and justice according to which any ethical dilemma in medicine can be analysed. In each specific case, the principles need to be specified and balanced to be able to analyse the concrete ethical problem and to search for a possible way to handle the ethical issue at stake. They offer criteria to consider, help to clarify the obligation to follow first and indicate the next step. In the following, we will illustrate the four principles and their relevance for analysing conflicts of obligations in the context of medical research.

The first principle to highlight is autonomy. Autonomy and the right to self-determination are the basis for the ethical and legal foundation of informed consent. In medical research, patients and other (potential) research participants must be informed and be able to decide voluntarily whether they would like to take part in a research project or not. In this context, mental capacity or competence is defined as the ability to understand and to be able to make autonomous decisions on the basis of the necessary information. However, autonomous decision-making is also relevant for decisions on the part of the medical researcher: For example, the researcher can be described as making autonomous decisions only if he or she is free to act on the available information. A concrete and practically relevant example is whether a clinical researcher is in a position to inform patients or test participants about the findings of interim analysis if such information may be relevant to the participants' decision whether to participate in the research or not. In the case of conflicting obligations in medical research, autonomy can be understood as supporting an adequate process of decision-making on the part of the patient, as well as the physician.

The principles of beneficence and nonmaleficence in medical contexts are often seen as one. However, when looking at situations outside the health-care system, we distinguish both principles. There is a morally relevant difference between preventing harm and doing good. Not doing harm is something we can claim from each other in a society. In fact, to interfere with the physical integrity of a person is sanctioned by law. In contrast we cannot require that people do good to each other.

In the medical setting, both beneficence and nonmaleficence are required by physicians and other health-care professionals. This double obligation can lead to conflicts in some cases. One example of conflicting obligations in this context may be considerations with respect to the welfare of patients who participate in a trial, and the welfare of all future patients who may benefit from the trial results. In this case, the future advantages gained by conducting a trial and the risk for patients (or test participants) during the trial conflict. In this instance, it is the duty of the medical researcher to identify and weigh possible benefits and risks (in the sense of possible harm). But how can these principles influence an analysis of conflicting

obligations in the setting of medical research? One important role of the two principles is that they can serve as criteria for good and reasonable consideration and judgement. They may help to find out which obligation has the primacy because they are able to clarify the conflicting obligations. However, they cannot solve the conflict on their own.

The fourth and final mid-level principle relevant to the analysis of conflicts of obligation in medical research is justice. This principle includes several aspects. According to the traditional interpretation, justice means equity, namely the equitable allocation of drugs and treatments and equal treatment, which means equitable care for each patient. Justice can also imply intergenerational justice, in other words, a fair treatment of current and future patients and of current and future society. In the context of conflicts of obligation in medical research, we will focus on a third aspect of justice, namely the equitable behaviour of physician researchers. It is one of the physician's duties to improve the quality of care. Thereby, every patient should have the same opportunity to gain access to physicians and their care.

> Physicians must individually and collectively strive to reduce barriers to equitable health care. (ABIM Foundation 2002)

As indicated above, conflicts of obligation in medical research often refer to the burdens and benefits of a clinical trial. In this case, the risks and benefits have to be distributed equitably. Therefore, equal shares of benefit or burden, a person's individual need, individual effort, merit and societal contribution seem to be relevant properties which should be regarded (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). In addition to this, the information gained by medical research has to be shared with all interested parties. Justice, more than the other principles, seems to be able to minimize or to solve a conflict of obligation, because it provides the opportunity and the criteria to evaluate the consequences following each obligation. With equal treatment and equitable allocation in mind, it is possible to identify the more important obligation.

In this section we have analysed conflicts of obligation in the context of medical research using mid-level ethical principles. It is due to the nature of conflicts of obligations and the respective ethical dilemmas that neither the four principles nor other ethical theories can solve such a conflict. However, the principles can at least help to clarify the ethical issues and, in the course of specifying and balancing the principles, it may become more obvious which obligation(s) needs to be followed primarily.

10.4 Conflicts of Interest in Medical Research

Following the definition of conflicts of obligation and the description of the ethical contribution of the four ethical principles to clarify conflicts of obligation and to give advice on the next steps, we will now focus on the issue of conflicts of

interest. These kinds of conflicts pose another challenge because, in contrast to the conflicts of obligation, conflicts of interest focus, on the one hand, on primary interests according to the physician's ethos or moral duty. Actions which are in accordance with the above-mentioned obligations can be seen as actions which further the primary interests of medicine: To do patients good and to avoid harm and also to empower patients to make autonomous decisions are examples in this respect. On the other hand, there are secondary interests, which are often types of self-interest and which may influence health-care professionals' action in terms of compromising the primary interests (Thompson 1993; Morreim 1995). Examples for such secondary interests are financial interests, and also an interest to promote one's academic career. It is important to note that secondary interests are not per se bad interests. In fact, they contribute considerably to advances in medicine. However, these interests are subordinated to primary interests not least due to the vulnerability of patients and related duties on the part of health-care professionals.

The challenge for the health-care system is not only to recognise these conflicts, but also to minimize them and to explain why following self-interests should not be at the centre of health-care professionals' work. Our analysis indicates that although the term "ethics" is frequently used in publications on conflicts of interest in patient care and medical research, there is a deficit of ethical analysis in the sense of ethical foundation and evaluation relevant to conflicts of interest.

To identify conflicts of interest and to provide a foundation for the call for regulation of conflicts of interest, it is helpful to base the considerations on ethical principles. In this respect the four principles of autonomy, beneficence, nonmaleficence, and justice underline the primary interests and obligations in medicine. In the following, we will focus on three more ethical principles which are relevant to the ethical analysis of conflicts of interest. According to the obligations in the health-care system, the principles work as a verification of the value of the primary interests; their job is also to justify actions regarding conflicts of interest in the health-care system.

The first principle frequently mentioned in connection with conflict of interest regulation is professional integrity. Professional integrity is directed at physicians' honesty. In this sense, it is closely associated with physicians' ethos and medical professionalism. To act with integrity is part of the self-concept of a physician. To act professionally and in an upright way thus means to act in accordance with honesty, truthfulness and accuracy. In the context of medical research, professional integrity may be specified in terms of clinical researchers who put the primary interests of medicine before their own interests. A concrete example would be the clinical researcher's behaviour when considering a patient as a participant for his or her study who may profit more from individualized treatment outside a clinical trial. In contrast, acting without integrity injures the profession's reputation and one's own reputation as a physician, and may jeopardize the confidence society has in physicians.

The second principle connected with professional integrity and medical professionalism is that of confidence. Confidence thereby means, on the one hand, people's trust in physicians and their behaviour and, on the other hand, the

physicians' pledge to justify this trust. Betraying people's trust will affect the physician himself/herself, the profession and the trust in the physicians' ethos. To prove oneself as worthy is also part of the self-concept and of professional behaviour. A physician can prove himself/herself worthy when he/she focuses on the primary interests in patients' welfare and when his/her actions correspond to these interests. The physicians' ethos can only work while people trust physicians. Therefore, people's confidence that physicians will act according to their obligation in the health-care system is an important point.

The third ethical principle important in the context of conflicts of interest is transparency, which is well known in the discourse on ethics in science and the humanities (Bayertz 1991). Its goal is to verify and reconstruct processes (e.g. design of a clinical trial) and respective outcomes (e.g. publication of the trials' results). In the context of conflicts of interest, transparency means to act in a transparent and verifying way. True and transparent information is a requirement for autonomous and just decisions. Physicians, for example, cannot really make autonomous and just decisions if there is no transparency with respect to the quality and possible bias of the information on which they base their decisions. Furthermore, transparency is able to guide the decisions about the management of conflicts of interest. The call for disclosure of conflicts of interest is often connected with the call for transparent information and publication. Although transparency is not a typical ethical principle, its profit lies in its potential to control a lot of influences on physicians or others concerned. In this respect, the principle serves as a foundation for the demand to disclose biases, to manage recommendations on behaviour and to suggest a solution to handle conflicts of interest. Moreover, and in contrast to other principles which directly argue for primary interests, transparency is able to identify the conflicts and the difference between primary and secondary interests. Transparency demands the disclosure of all relevant interests and, thereby, enables an informed judgement about a conflict of interest. Against this background, transparency can be seen as a precondition with respect to other ethical principles (e.g. autonomy) and, at the same time, the principle serves as a basis for the management of conflicts of interest.

10.5 Revisiting Conflicts of Interest: An Ethical Analysis of the Concept and of Regulation Strategies

When facing a conflict of interest, one could assume that there are no problems when primary interests are being followed, underlined by the four principles and the principles of professional integrity, confidence and transparency. However, it seems that, following the identification of a conflict of interest, the actual work only starts because it is then necessary to judge the present conflict and to suggest concrete management. Against this background, the purpose of this part is to critically review the concept of conflicts of interest and to analyse its implications with a focus on management strategies.

As mentioned in the introductory part of this chapter, using Morreim's (1995) and Thompson's (1993) definitions of conflicts of interest as compatible means an equation of "primary interests" with one's "obligation", and "secondary interests" with "self-interest". However, such an equation merits further analysis. For the second part of the definition, we can expect that secondary interests and self-interest both lead to one direction of ethical analysis. In most cases, secondary interests in financial, social or intellectual incentives are directly motivated as self-interests. From this point of view, the equation of both terms is acceptable. However, and as it has already been pointed out, one has to be careful not to equate secondary interest with bad interest. They cannot only be perfectly acceptable, but highly relevant in order to pursue primary interests. The interest in an academic career in medicine, for example, may generate important knowledge for the medical community.

Unlike the acceptable equation of secondary interests and self-interests, it seems more difficult from an ethical perspective to equate "primary interests", used in Thompson's (1993) definition of a conflict of interest, with "obligations", used by Morreim (1995). The difficulty is due to the association of obligations with specific roles (e.g. physicians, nurses or other professionals). In contrast, interests seem to be defined, on the one hand, through personal values according to one's own moral sense and, on the other hand, based on values of a system or an institution. To put it in other words, the term "primary interest" compared to "obligation" is more open in its meaning regarding individuals with valuable interests or institutions with special interests. In the latter case, the primary interest might become an obligation to those working, for example, in the medical system. While obligations most often target people with a special profession and codex, primary interests may be related to special (and also personal) values. Following this analysis, we suggest that Morreim's definition distinguishes physicians' duties and responsibilities versus subordinated self-interests more clearly. In contrast, Thompson's definition of primary and secondary interest either must be read as being valid within a special system, or it runs the risk of being misunderstood as distinguishing interests without clarifying the point of reference for the distinction. Even if we assume that the distinction between primary and secondary interests is context-specific, we face the challenge that we need to agree on what to count as primary or secondary interest in a specific situation and how to react when there is a conflict between such interests.

This leads to the last point. Guidelines and other strategies to handle conflicts of interest currently focus on disclosure. Proponents of such strategies often emphasise that conflict of interest policies are more about constellations in which primary interests may be compromised. However, one may ask what such guidelines can contribute to the effective promotion of ethical behaviour and what else is necessary to consider. In this context, it seems important to pay more attention to specific situations, cases and individuals in conflicts of interest. Transparency and disclosure facilitate the identification of conflicts of interest. Furthermore, these strategies could stimulate physicians and other parties to think about the meaning of primary and secondary interests and related conflicts in their

context. However, in the end, it seems necessary to establish concrete frameworks according to which the facts and values related to a specific conflict of interest are analysed. Besides the ethical principles mentioned in this paper, the risk of influenced judgement, as well as possible consequences for medical research or other domains in medicine, have to be taken into account (Komesaroff and Kerridge 2011; Lo and Field 2009; Strech and Knüppel 2011; Lieb et al. 2011).

10.6 Concluding Remarks

The term "conflict of interest" is often used rather vaguely and for different ethical conflicts in medicine. This is especially true for conflicts between two obligations of equal measure, and for conflicts between primary and secondary interests. We have seen that the role of mid-level ethical principles differs considerably with respect to conflicts of obligation, on the one hand, and conflicts of interest, on the other. Ethical principles may help to clarify the obligations and their relatedness to the case and help to balance the obligations and duties in order to decide on what to do next. However, the principles per se cannot solve such a conflict—they can only give hints on what to do in this dilemma situation. In the context of conflicts of interest, the job of ethical principles is to underline the value of the primary interests and to support recommendations regarding the management of these conflicts. When revisiting the concept of conflict of interest from an ethical perspective, it becomes clear that the existing definitions cannot be used interchangeably. Further clarification of the meaning of conflict of interest is not only necessary with respect to the need for a clear concept, but also with respect to the implications for an appropriate and effective management of conflicts of interest in medicine. In the ongoing debate about the contribution of ethical principles and about the strategies needed to handle a conflict of interest, more precise considerations might be necessary to find out useful or important strategies. This article illustrates some hints concerning the current considerations.

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Chapter 11
Research Ethics in Genomics Research: Feedback of Individual Genetic Data to Research Participants

Annelien L. Bredenoord and Johannes J. M. van Delden

11.1 Introduction

An important topic of debate in (clinical) research ethics is whether respect for research participants implies that results should be returned to them (Shalowitz and Miller 2005). In the context of genetics research, the evolving debate resulted in the majority view that individual genetic data should be disclosed to research participants when these data are of clinical relevance, i.e. preventive or therapeutic measures are available (UNESCO 2003; WHO 2003; Knoppers et al. 2006). Let us call this the "clinical utility standard". Several changes in the (genetic) landscape, however, have challenged the feasibility and appropriateness of the clinical utility standard.

Firstly, genetics research has shifted from Mendelian genetics to genomics research. Genetics research is focused on the identification of rare monogenetic mutations with a high predictive value. Genomics research is focused on identifying risk factors for complex common diseases, such as cancer, diabetes and heart disease. Although these so-called multifactorial disorders frequently occur, the possible (set of) genes underlying these disorders only partly explain the occurrence of the disease (Quigley and Balmain 2009). Another characteristic of genomics research regards its large-scale character: large sample sizes and large amounts of genetic data, requiring the participation of large numbers of research subjects.

Secondly, genomics research has been fuelled by the rapid developments in next-generation sequencing technology. During the last few years, genomics has been characterised by genome-wide association studies (GWAS), which are aimed

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at finding genetic variations that contribute to common, complex diseases. By comparing the DNA characteristics of people with a disease with a matching control group, genomic loci that are associated with health and disease are identified. Moreover, researchers now increasingly deploy whole genome sequencing (WGS) methods, which entail the sequencing of the entire DNA of an individual to generate personal genomes. Although WGS is predominantly used in the context of clinical research, WGS methods are emerging for diagnostics in the clinical context as well (e.g. Ashley et al. 2010). It has the potential to generate unequalled amounts of genetic data both in quantity and significance (Kaye et al. 2010). This implies that the generation of many known and unknown genetic variants in individual participants of genetics/genomics research as intentionally or collaterally obtained by-products is unavoidable, including genetic variants that were outside the focus of the study (Bredenoord et al. 2011a).

A third development concerns the emergence of biobanks. Although biobanks come in multiple varieties (they vary with respect to the type and number of tissues stored, the extent of genetic, clinical and personal data, and the permitted use of the samples and data), they can, on a general level, be defined as "libraries" or collections of human biological samples matched with phenotypic data. Many biobanks do not yet have disclosure policies or their policies differ—which complicates the collaboration between biobanks.

A fourth development concerns the commercial activities in the field. Internet-based direct-to-consumer companies offer genetic tests that are marketed to consumers outside the scope of the healthcare system. Although many people have raised concerns about the quality of the services offered (including the quality of the genetic test, the quality of the laboratory and the information provision) (ESHG 2010), the existence of these companies at least shows that people are willing to pay in order to learn about their genetic constitution. This is of relevance for our discussion, as it may indicate that people may be interested in having feedback of (or at least access to) genetic results.

In spite of an extensive debate, there remains a lack of consensus regarding when and how to disclose individual genetic data to research participants in studies with a genetic component. As a consequence, researchers and institutional review boards (research ethics committees) continue to struggle with the question as to whether research protocols should adopt provisions about the return of genetic data, and if so, how this should take shape. Clearly, it is time to rethink the scope and limits of the clinical utility standard in order to make it appropriate for medical-scientific research involving human subjects in the genomics era. In this paper,[1] we will firstly review the debate regarding feedback of individual genetic

[1] This paper is partly based on Bredenoord AL, Onland-Moret NC, van Delden JJM (2011a) Feedback of individual genetic results to research participants: In favor of a qualified disclosure policy. Human Mutation 32:1–7, and Bredenoord AL, Kroes HY, Cuppen E, Parker M, van Delden JJM (2011b) Disclosure of individual genetic data to research participants: The debate reconsidered. Trends in Genetics 27(2):41–47.

data, and subsequently, argue in favour of a qualified disclosure policy. We will end with questions that warrant further ethical debate.

11.2 Clarifying the Debate

The discussion regarding disclosure of genetic research results has not been whether people should have (passive) access to their personal data. After all, the right to have access to one's personal, genetic and medical data is recognised in many international and national legal guidelines, at least in the European context. The discussion has also not centred on the question whether people should receive the main study results on an aggregate level. After all, although it does not happen everywhere on a regular basis, it is a rather uncontroversial practice to offer research participants the opportunity to receive a mailing with the main findings of the research project in which they participated (Bredenoord et al. 2011b). The main discussion is whether people should receive feedback on their individual genetic data. Obviously, a necessary condition for individual disclosure is that the data can be linked to a specific research participant. The discussion, therefore, does not apply to research using anonymous samples and data.

Our analysis of the literature shows that the extreme positions of "no disclosure whatsoever" and "full disclosure" are seldom defended (Bredenoord et al. 2011b). The overwhelming majority of commentators defend either a very restrictive disclosure policy or an intermediate position of qualified disclosure. Below, we will firstly discuss (and predominantly reject) the arguments that have been put forward to support a restrictive disclosure policy, which means that genetic research results should not be returned to individual research participants with an exception for life-saving data (Melzer 2006). Subsequently, we defend a qualified disclosure policy.

11.3 Arguments Against Disclosure of Other Than Life-Saving Data

11.3.1 Disclosure Promotes the Therapeutic Misconception

The most prominent argument supporting a restrictive disclosure policy contends that blurring the distinction between research and clinical care has the potential to lead to a therapeutic misconception, which arises when a research participant mistakenly believes that the research project's primary aim is therapeutic (Applebaum and Litz 2008). This is important, because therapy and research are not governed by the same goal. Whereas therapy aims to advance the individual patient's best interests, the nature of the research design (randomization, double

blinding) has, as its overarching purpose, to yield scientifically accurate, generalizable knowledge. Disclosing individual results would, according to proponents of this argument, conflate this distinction between therapy and research. As a consequence, participants may suffer from the therapeutic misconception and researchers may be inclined to overstate the benefits of enrolment (Clayton and Ross 2006).

Actually, people only suffer from the therapeutic misconception when they "mistakenly" believe that the research project they are about to enter will benefit them directly (Bredenoord et al. 2011a). This could indeed be the case in genetic association studies, as these are likely to find common genetic variations that are associated with a particular phenotype with low or modest effect sizes. In contrast, in studies that deploy WGS methods, the chances may be greater that new variants are found that give rise to a significantly increased disease risk (Ashley et al. 2010). Hence, whether people rightly think the research project could benefit them also depends on the type and aim of the genetic study and the methods used.

The blurring between research and clinical care does not necessarily have to be negative if appropriately recognized and measures are taken. Moreover, it may increasingly occur in the context of biobanks and WGS, where research and clinical care are more and more intertwined. Although the therapeutic misconception is a persistent phenomenon that may not be precluded entirely, we do not consider this an a priori argument against disclosure.

11.3.2 Disclosure Rests on a Mistaken Interpretation of Autonomy

Those supporting a restrictive disclosure policy disagree that showing respect for a participant's autonomy necessarily requires disclosure. Respect for participants means treating human beings capable of self-determination as autonomous agents. It also requires researchers to provide all the information about the trial, allow people to enrol and withdraw, etc. According to this argument, however, it does not require them to actively disclose individual research results to the participants (Melzer 2006).

Actually, whether showing respect for a participant's autonomy indeed supports disclosure depends on how one understands autonomy (Bredenoord et al. 2011a). Autonomy, in a negative interpretation, is most commonly understood as the individual's right to make their own decision without interference or coercion from others (Berlin 1969). From this perspective, researchers can deploy a very restrictive disclosure policy (i.e. only returning life-saving data) and, at the same time, respect a participant's autonomy, as long as participants are well-informed about the restrictive disclosure policy, have an adequate understanding and no coercion or undue influence has occurred. In a positive account, autonomy entails the ability to take control of one's life and to live according to one's values and

beliefs (Berlin 1969). From this perspective, autonomy also entails maintaining or fostering people's capacity for autonomy (Feinberg 1987). If we interpret the duty to respect autonomy in a positive account, then this indeed forms a ground to support disclosure of genetic research results. After all, people may use information about their genetic make-up to take control of their lives and realise or adjust their life-plans.

11.3.3 Disclosure Would Impose an Untenable Burden on Research Infrastructure

Another argument put forward to support a restrictive disclosure policy holds that the practicalities in returning results may impose untenable burdens on the existing research infrastructure. Enabling disclosure requires a careful administration, counselling services, possibly re-testing in a clinical laboratory, and so forth. This could imply that resources that could be used for research are used for disclosure. In addition, it could make unreasonable demands on researchers.

We indeed agree that there are limits on what we can reasonably expect from researchers and research teams. Obviously, any effort to provide feedback should be in sound proportion to any possible benefits of feedback (Bredenoord et al. 2011a). Although not an overriding objection against disclosure, this is certainly something that should be taken into account in any disclosure policy.

11.3.4 Disclosure is Not Feasible

A fourth argument in favour of a restrictive disclosure policy holds that disclosure would not be feasible. Feasibility is questioned for two reasons (Bredenoord et al. 2011b). Firstly, it is questioned whether research participants are able to make a selection out of the wide array of possible genetic results. This is predominantly due to the character of genetic findings, which are often probabilistic and/or pleiotropic. Pleiotropy is the ability of a single gene to influence multiple traits or conditions, which presents the possibility that acquisition of genetic information about one condition either at the same time, or in the future, provides information about a different condition (Cooper et al. 2006). An additional difficulty would be that people are not very familiar with biomedical research in general and genetics in specific. These factors together challenge a proper understanding and the possibility to make a reasonable selection.

Secondly, it is questioned whether researchers are and should be capable of selecting and communicating genetic research results. They are trained to do research, which is a completely different competency than helping people understand genetic information and communicate genetic findings. If researchers have a duty to return results to participants, this may create an unreasonable and

unmanageable precedent. To what extent is it reasonable to ask researchers to meet such demands?

It will indeed be a challenge to help people making meaningful decisions, but people face complex decision-making in many facets of life and in many circumstances. Instead of disqualifying the positive conception of autonomy, we favour an approach in which the researcher (or another professional) makes efforts to help people understand the genetic information and, subsequently, to help them articulate their preferences regarding disclosure. Obviously, those efforts should (again) be in reasonable proportion to any possible benefits of feedback (Bredenoord et al. 2011a).

11.3.5 Disclosure has Harmful Consequences

A final argument supporting a restrictive disclosure policy is that disclosure of genetic information can have adverse psychological, financial and social consequences. People may feel anxious about knowing they have an increased risk of developing disease, or the genetic information may undermine someone's capacity to obtain insurance.

We agree that these potential harmful effects warrant a cautious approach. However, this argument does not provide a valid objection against disclosure as long as participants are adequately informed and society has taken sufficient measures to ensure access to insurance.

11.4 In Favour of a Qualified Disclosure Policy

Our discussion of the arguments supporting a restrictive disclosure policy shows that most arguments against a wider disclosure policy are not conclusive. Moreover, we have argued elsewhere that the principles of autonomy and beneficence provide justification for disclosure of genetic research results in addition to life-saving data of immediate clinical relevance (Bredenoord et al. 2011a). Disclosure may also have the favourable side-effect that people may become more engaged with biomedical research. In sum, valid reasons exist to state a duty to return individual genetic research results, but important competing duties and values need attention as well. We therefore arrive at a qualified disclosure policy (Bredenoord et al. 2011a). This is an intermediary approach in which researchers in consultation with the institutional review board (research ethics committee), clinicians and, preferably, participant representatives designate several "packages" for disclosure, or a "menu" of options (Rothstein 2006). This could be interpreted as a variant of generic consent, a concept introduced in the early days of genetic screening: A general consent providing sufficient information to make informed decisions but that avoids information overload (Elias and Annas 1994;

Health Council 2010). Our packages can be compared with the "panel" of screening tests proposed by Elias and Annas (1994).

A qualified disclosure policy contains a "standard" default package routinely and mandatorily offered, including life-saving information and genetic variants of immediate clinical utility. The default package makes use of an opt-out procedure, meaning that people will receive this information unless they have explicitly indicated they do not want to receive feedback. Such a default-based opt-out system is a variant of what Thaler and Sunstein (2008) coined "liberal paternalism": Liberalism in the sense that participants are still free to choose not to receive results, (soft) paternalism because we assume that people want to receive those results and, therefore, researchers should try to assist and influence the choices people make in order to make their lives healthier or better (Thaler and Sunstein 2008).

Whereas the default package "should" be offered, we propose three additional packages that "could" be offered (Bredenoord et al. 2011a). The first additional package contains data of potential or moderate clinical utility. Although disclosing these findings may still be clinically or personally useful, the benefits of offering this package are usually lower compared with the default package. As any disclosure policy contains a trade-off between potential benefits (and risks) of disclosure for the participant versus the harms of hindering research, the proportionality of offering this package is context-specific (Beskow and Burke 2010). Relevant factors are the significance of the findings (including the clinical utility of the results), the possibilities of the research team to provide feedback and the structure of the health-care system. The second additional package contains data of reproductive significance. Here, the proportionality of offering this package should also be taken into account. The third additional package contains data of personal or recreational significance. The existence of the previously mentioned internet-based direct-to-consumer companies shows that people can be interested in receiving genetic information, even though many genetic associations are unreliable or poorly predictive. Whether the trade-off between the benefits of disclosure versus the risks of hindering biomedical research is still in balance depends completely on the possibilities of the research team to provide feedback and the structure of the health-care system.

11.5 Should Researchers Actively Search for Genetic Data?

We hitherto assumed that only data intentionally or collaterally obtained as a by-product of genetic/genomic research should be returned. One might, however, argue here that, particularly with respect to life-saving data, researchers have a moral duty to actively search for those variants, as the efforts to actively unveil this information would stand in reasonable proportion to the benefits. The distinction made between the sequencing of the genome and the subsequent analysis of those data may be relevant here (Health Council 2010). Whereas whole genome "sequencing" results in raw sequencing data, whole genome "analysis" processes

these data into intelligible information. One could, therefore, consider routinely analysing a number of well-defined, high-risk, life-saving variants.

There are, however, a number of arguments against stating a duty to actively search for genetic variants. Firstly, the amount of eligible variants currently available is quite limited, which implies that an infrastructure has to be designed for actively searching, documenting and returning variants, while probably only a small number of people will benefit. After all, the likelihood of finding a causal single gene variant possibly eligible for disclosure will be extremely low (Janssens and Van Duijn 2010). At the moment, therefore, this would pose an unreasonable burden on researchers. In addition, such an offer to actively search for life-saving data may lead participants to believe that it is likely that the study generates those well-defined, high-risk, life-saving data. In other words, it may promote the therapeutic misconception. Thirdly, actively searching for genetic data would also not be in line with current practice in other forms of clinical research. In research making use of an MRI-scan, for example, participants are never offered a full body check. If, however, by chance, something suspicious is observed on the scan, researchers refer the participant to a health professional. Similarly, one could adhere to the distinction between returning genetic data obtained as a by-product of research, and actively searching for genetic information. Nevertheless, one could imagine that this distinction will shift due to technological advances. When an active search for genetic variants only encompasses one symbolic "push on the button", the proportionality argument will become weaker. Therefore, although researchers should currently not actively search for genetic variants, this conclusion may be revisited due to technological advances.

11.6 Concluding Remarks

The hitherto often deployed clinical utility standard, where genetic data were returned when these data were of clinical relevance, is not sufficiently fine-meshed for the genomics era. Genetics/genomics research has become too complex and too varied to deploy a "one size fits all" standard for disclosure of research findings. We therefore propose to use a more refined, qualified disclosure policy which makes use of packages. The standard default package should be offered routinely and contains life-saving information and genetic variants of immediate clinical utility. Whether (one of) the three additional packages should be offered is context-specific and should be decided on a case-by-case basis. Such a qualified disclosure policy, in our opinion, best balances the benefits and harm of disclosure. From a participant perspective, it acknowledges the importance of autonomy and beneficence, and the normative component of result appraisal. By offering packages, it also acknowledges the difficulties people will have with unrestricted result selection. It, on the other hand, acknowledges that the efforts to realise disclosure will be relatively high, while the benefits of disclosure are expected to be low, which poses an unreasonable burden on research infrastructure (Bredenoord et al. 2011a).

We have offered the moral underpinning and the general outline of a qualified disclosure policy; now the following issues need to be elaborated further.

Firstly, the packages need to be refined and filled in—and this is predominantly a task for the genetics community. Subsequently, the packages can be tested in an experimental setting. Secondly, empirical studies are necessary to find out what results participants find useful and relevant, and how results should be communicated. One could, for example, experiment with a more active involvement and engagement of participants and biobank donors using educational tools and social media. Internet communities may realise interaction between participants and researchers, thereby reducing the limitations of generic consent, as those people requiring more specific and in-depth information on which to base their decision can obtain this in an approachable way (Bredenoord et al. 2011a). Additionally, the inclusion of genetic counsellors may benefit the comprehension and communication of genetic data (Zierhut and Austin 2011).

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Chapter 12
Regulating "Higher Risk, No Direct Benefit" Studies with Children: Challenging the US Federal Regulations

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12.1 Introduction

Some studies necessary for improving medical care for children cannot directly benefit the children involved. Many observational studies and early-phase drug development studies, for example, do not directly benefit their subjects. Involving children in such studies is an ethically complex question. Given the assumption that children cannot give informed consent, it is difficult to justify exposing them to the inherent risks and burdens solely for research purposes; yet, a total ban on such studies could have a detrimental effect on the development of treatments for sick children in the future. As a compromise, in order to ensure that individual research subjects are protected, while also allowing important paediatric research to occur, most countries have chosen to allow review boards to approve paediatric research without direct benefit if the risks and burdens do not exceed a certain threshold. Generally, the risks and burdens of such research may not be more than "minimal" (in the absolute sense of the word).

The European Convention on Human Rights and Biomedicine and the Declaration of Helsinki, which are the two relevant ethics documents recognised in Europe, do not allow review boards to make exceptions to the requirement of minimal risk and burden (Council of Europe 1997; World Medical Association 2008). Our analysis of the decisions of the Dutch Central Committee on Research with Human Subjects (CCMO) revealed that this approach sometimes requires review boards to reject what they think are important studies (Westra et al. 2010a). During the period analysed, for example,

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several early-phase drug development studies were dismissed for involving risks and/or burdens above the minimal level. Some observational studies involving magnetic resonance imaging (MRI) procedures in children younger than 5-years old were also rejected due to their risks and/or burdens: Scanning children in this age group with the use of sedation, which is the common clinical practice, was considered to involve more than minimal risks; scanning without sedation, on the other hand, would impose a more than minimal burden on the subjects.

Our analysis revealed that review boards occasionally find ways to approve important studies that should formally be rejected: The concepts of "minimal risk" and "minimal burden", if not accurately defined, are ambiguous enough to allow for far more permissive interpretations in cases of studies that are considered very important. The CCMO, for example, approved a "proof of principle" study in children with Duchenne muscular dystrophy despite the fact that it involved a muscle biopsy, a procedure that is usually considered to involve more than minimal risks and burdens (see boxed text 12.1) (Van Deutekom et al. 2007; Westra et al. 2010a). The committee had to stretch the meaning of the concepts to approve this study.

Boxed Text 12.1 Example Study

Duchenne muscular dystrophy is a disease associated with severe, progressive muscle weakness leading to wheelchair dependency and early death at the age of 20–35 years. Currently, there is no treatment available except for ventilation techniques and drugs that may improve fitness and prolong mobility. Antisense oligonucleotides have recently been shown to restore dystrophin expression in animal models. This study explored the safety and local effects of one antisense oligonucleotide in four children aged 8–16 years (in older patients more muscle tissue has been lost, which rendered them unfit for participation). The children were not admitted to the hospital but had to visit the hospital several times to undergo invasive procedures: The drug was injected at four sites and the local effects were evaluated by means of a muscle biopsy. The results of this "proof of principle" study were positive. However, no direct benefits for the subjects were involved because the effect was limited to only one of their many muscles. Future studies will have to reveal whether it is also safe and effective to administer antisense oligonucleotides systemically.

We think that clear definitions of "minimal risk" and "minimal burden", along with openness about possible exceptions to these requirements, are better than downplaying certain risks and burdens or than considering doubtful benefits as direct benefits for the sake of being able to approve the trial. It may well be that higher levels of risk and burden can occasionally be ethically justified. However, when such exceptions are made, they must be made explicitly, and the reasons for doing so must be transparent and reviewable.

In a recent document that provides guidance on the application of the European Clinical Trials Directive to trials with minors, a European Union ad hoc group has

hinted at following the US Federal Regulations (European Union 2008; European Parliament 2001). The US Federal Regulations offer two possibilities for approving studies with more than minimal risks and/or burdens; which from this point forward we will call "higher risk, no direct benefit" studies. Firstly, institutional review boards (IRBs) may approve studies that concern the subjects' disorders or conditions and that do not involve more than a minor increase over minimal risk. Secondly, "higher risk, no direct benefit" studies may be approved after review on a national level (see boxed text 12.2) (US Department of Health and Human Services 1983).

Boxed Text 12.2 The Relevant Parts of the US Federal Regulations

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

The Department of Health and Human Services (HHS) will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;
(b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psycho logical, social, or educational situations;
(c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
(d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) The IRB 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; and
(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
    (1) That the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or
    (2) the following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
(ii) the research will be conducted in accordance with sound ethical principles;
(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

This paper explores whether Europe should follow the US Federal Regulations completely or should instead adopt a modified policy. To critically evaluate the two possibilities described in the US Federal Regulations, we will first explore the ethical grounds for accepting only minimal risks and burdens, and then analyse whether and when exceptions to this requirement can be justified.[1]

12.2 Ethical Grounds for Accepting Minimal Risks and Burdens

Before discussing when or whether exceptions to the minimal risk and burden requirement can be ethically justified, it is essential to initially review the background of this requirement: What are the ethical grounds for accepting only minimal risks and burdens in the context of paediatric research without direct benefit? This question can actually be divided in two parts: (1) How can paediatric studies without direct benefit be ethically justified if they involve exposing children to risks and burdens solely for research purposes; and (2) why should the research risks and burdens in this context not be more than minimal? In this section, after introducing the problem, we will explain which justification for paediatric research without direct benefit we believe is most convincing. We will also explain why that line of justification can justify minimal risks and burdens, but, generally, not more than that.

The problem underlying the first question is related to the fact that children are considered unable to provide their voluntary and knowledgeable permission to participate in a study. Provided that all other requirements for ethical research (e.g. a relevant research question, fair subject selection, sound scientific design) are fulfilled, exposing competent adults to research risks and burdens solely for research purposes is considered acceptable if these adults give their informed consent (Emanuel et al. 2000). Exposing children who cannot give such an informed consent to undergoing research risks and burdens solely for research purposes involves the risk of using them merely as a means (Ramsey 1970).

Clearly, parents or other caretakers can make decisions on behalf of their children. Some people have argued that such proxy consent should be regarded as

[1] The results of this analysis have already been published in the American Journal of Bioethics (Westra et al. 2010b).

being as weighty as informed consent: Parents can make many decisions for their children free of state intervention, and so why should this not be one such decision (Ross 1997)? However, it seems problematic to allow parents to give proxy consent for risky activities that are not in the interests of their children (Ramsey 1970, 1976). Moreover, enrolling children in studies that cannot directly benefit them is not only the family's concern, but researchers and wider society are also involved, and they do not have the authority to expose children to the risks and burdens of research purely for the benefit of others (Wendler 2010). Researchers and society need an independent reason to judge the action as appropriate (Wendler 2010).

Allowing children to be involved in studies that cannot directly benefit them only if the risks and burdens are minimal may reduce the ethical concerns at stake, but does not eliminate them: Even studies with minimal risks and burdens still involve some risks and burdens. This, of course, depends on the definitions used: Very stringent definitions of "minimal risk" and "minimal burden" could completely eliminate all risks and burdens (Council of Europe 2005). Such definitions, however, go too far (Wendler 2005). The US definition of minimal risk (using an umbrella concept of risk that also includes the research burden) seems to allow, for example, for venipunctures, lung function tests and hospital admissions (European Union 2008; National Human Research Protections Advisory Committee 2010; US Department of Health and Human Services 1991; Westra et al. 2011). The definitions that we have recently proposed, which we believe are an improvement on the US definition, do also allow for such procedures (Westra et al. 2011). Thus, even in cases of minimal risks and burdens, the question remains how to justify exposing children to these minimal risks and burdens solely for research purposes.

The line of justification that we consider to be most convincing is that it can be in the broader interest of children to contribute to valuable medical research studies, because once they have grown up, they may come to embrace these contributions. That is, the subjects may later view their contributions as a valuable experience in their lives (Redmon 1986; Wendler 2010). Of course, we can never be certain that children will come to embrace their contributions to research: They may disagree with the value of the project and, even if they agree with the value of the project, they may rather not have contributed. These are the very two reasons for asking for informed consent of competent adults, and for accepting "no" as an answer. However, the fact that children may come to embrace their contributions, means that exposing them to research risks and burdens for the benefit of others is not necessarily the same as using them merely as a means.

This line of justification can justify the minimal risks and burdens mentioned, but, generally, not more than that (Wendler 2010). There are two reasons for such a restrictions. Firstly, the contribution is, in particular for very young children, purely passive: Young children do not understand the project to which they are contributing, are not involved in the decision-making process and sometimes do not even know that they are research subjects. Wendler (2010) convincingly explains how contributions, despite being passive, can be relevant to the interests of the individual contributing, but acknowledges that contributions that occur through an individual's agency say a great deal more about that individual's life

than purely passive contributions. The second reason is the above-mentioned fact that it is inherently uncertain whether children will eventually come to embrace their contributions.

12.3 Ethical Grounds for Allowing Exceptions

What about studies that involve higher levels of risk and/or burden? As we argued in the introduction, categorically rejecting such studies may have far reaching consequences, such as hindering drug development for children. Fortunately, the above-mentioned way of justifying minimal risks and burdens seems to allow some exceptions: It seems that both reasons for accepting only minimal risks and burdens do not apply to all studies and all children to the same extent.

12.3.1 Children Who Can Give Their Assent to Participate, Will Not Contribute Purely Passively

The first reason for accepting only minimal risks and burdens we mentioned was that children's contributions are purely passive. However, this reason does not hold for older children: With increasing age, children are increasingly capable of understanding the proposed study and of making their own informed decisions. The US Federal Regulations, and many other codes and regulations, acknowledge this developing autonomy by requiring assent (positive agreement) from those children who are considered able to give it, in addition to parental permission (European Union 2008; Council for International Organizations of Medical Science (CIOMS) 2002; US Department of Health and Human Services 1983; World Medical Association 1964). When viewed in conjunction with this parental permission, it becomes clear that children do not need to meet all the requirements for informed consent to be considered capable of giving their assent: They must be generally capable of understanding the study and of making their own decisions based on this knowledge (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1977). In its report "Research involving children", the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (US National Commission) has suggested that this means that assent should be required from children 7 years of age or older (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1977).

Although this concept of child assent has only be used in the context of the informed consent procedure so far, it also seems an ethically relevant factor when considering allowing exceptions to the requirement of minimal risk and burden. In the case that children are generally capable of understanding the study and of making their own decisions based on this knowledge, there seems to be less need to restrict the research risks and burdens to which they may be exposed.

12.3.2 Contributions to Exceptionally Valuable Studies are More Likely to be Embraced

Let us consider the second reason for accepting only minimal risks and burdens: That it is uncertain whether children will eventually come to embrace their contributions. Again, this possibility is not in all cases equally uncertain. The likelihood depends on the characteristics of the subjects: Not all children are equally likely to come to embrace their contribution. In addition, the likelihood depends on the value of the study at stake. Not all studies are equally valuable; thus, they are not equally likely to be embraced.

12.3.2.1 Characteristics of the Subjects

Relevant characteristics of the subjects are their ability to give their assent to participate in the study, their individual character traits and their life expectancy. The subjects' ability to give assent seems a strong embrace-predictor: It can be expected that children who have consciously agreed to participate in the study are well on their way towards fully embracing their contribution. If an appropriate cut-off age can be agreed upon, this characteristic could also easily be translated into policy. However, the subjects' ability to give assent has already been previously identified as a factor that is ethically relevant when considering allowing exceptions to the requirement of minimal risk and burden.

The two other subject characteristics may also be relevant embrace-predictors, but cannot easily be translated into policy. Individual character traits, for example, however important in principle, cannot be taken into consideration, because review boards must do their job before the study is initiated, and hence they only know the group-level characteristics of the subjects who will be enrolled in a study. Life expectancy is a complex issue: In older children, a short life expectancy could increase their desire to contribute to something valuable; in younger children, however, a short life expectancy mostly implies that they will not reach an age at which they might fully embrace their contributions.

12.3.2.2 The Value of the Study

The likelihood of the subjects coming to embrace their contribution also depends on the value of the study. We believe that some studies are exceptionally valuable, and that two issues play a role. Firstly, for a study to be exceptionally valuable, the desired data must be truly indispensable for improving medical care for children. Although not allowing exceptions to the requirement of minimal risk and burden may hinder indispensable studies, it is unfortunately not true that all proposed studies are truly indispensable. This is an actual problem in the context of paediatric drug research, as some proposals for paediatric drug research may have more to do with market considerations than with the needs of the patients. Often, several treatment options

for the disease at stake are already available. In such cases, additional treatment (or diagnostic, or preventive) options may be welcome, but are not truly indispensable. Moreover, by using available evidence and/or modelling approaches, proposed studies can occasionally be avoided (De Wildt and Knibbe 2009; Tafuri et al. 2009). Recent stimulation programs for paediatric drug research seem to contribute to the problem: The extended market exclusivity at stake can lead the pharmaceutical industry to focus on drugs with large adult markets but only limited application in children (Boots et al. 2007; Budetti 2003; Jong et al. 2001; Pandolfini and Bonati 2008; Permanand et al. 2007; Tafuri et al. 2009).

Secondly, if it is to be exceptionally valuable, a study must have the ideal design for obtaining these data as compared to all other possible designs. This is the case, we believe, if the study design encompasses the optimal balance between scientific rigor and an optimal risk–benefit ratio for the research subjects. Thus, the methodology should be of excellent quality, and the subjects should not have to face more risks and burdens solely for research purposes than strictly required to obtain the desired data. This is not always the case: Sometimes the desired data could also be obtained with direct benefits to the subjects, with less vulnerable subjects and/or with lower levels of risks or burden, either within the proposed study or within a completely different study design. In principle, review boards are assigned to judge whether proposed studies are acceptable rather than ideal. Yet we are of opinion that when research requires children to face more than minimal risks and burdens for the benefit of others, the study should be ideal rather than acceptable.

The Duchenne study (described in boxed text 12.1) provides a good example of a study that fulfils both of these criteria, and so can be regarded as exceptionally valuable. This study was an essential step towards developing a drug for a yet-incurable disease. Also, it seems to have involved the ideal design for obtaining the required data: It was clearly impossible to get the proof of concept within a design offering direct benefit the subjects, or with older subjects, and all study procedures were essential to obtaining the data.

We believe that contributions to such exceptionally valuable studies are significantly more likely to be embraced. Thus, we believe that the value of the study, encompassing both the indispensability and the ideal design of the study, is the second factor that is ethically relevant when considering allowing exceptions to the requirement of minimal risk and burden.

12.3.3 Together, the Two Factors Seem Sufficiently Weighty

We have identified both the assent of the research subjects and the value of the study as factors that are ethically relevant when considering allowing exceptions to the requirement of minimal risk and burden. Taken individually, these two factors do not seem to offer sufficient grounds for exposing children to higher levels of risk and burden: Assent acknowledges the developing autonomy of the child, which means that children who are able to give assent still need extra protection compared to adults, and the chance that children will come to embrace their contributions remains a matter

of uncertainty, even when the study is exceptionally valuable. However, when taken together, the two factors appear sufficiently weighty. Thus, "higher risk, no direct benefit" studies can be considered acceptable in cases where the subjects are able to give their assent to participate in the study and the study is exceptionally valuable.

12.4 The US Federal Regulations

In the previous two sections, we explored the ethical grounds for accepting only minimal risks and burdens and have identified two factors that can justify making exceptions to this requirement. We will now critically evaluate the two possibilities for approving "higher risk, no direct benefit" studies as described in the US Federal Regulations. According to Part 46.407 of these regulations, such "higher risk, no direct benefit" studies may be approved after review at a national level. According to Part 46.406, IRBs may approve "higher risk, no direct benefit" studies that do not involve more than a minor increase over minimal risk (see boxed text 12.2).

12.4.1 The Selection Criteria

"Higher risk, no direct benefit" studies must fulfil several criteria to be approved under Parts 46.407 or 46.406 (see boxed text 12.2). The main selection criteria (46.407-a and 46.406-c) seem to be related to the value of the study. However, both criteria are based on rather general words, which makes it uncertain whether they will be able to successfully select studies that can be regarded as exceptionally valuable. The 46.407 criterion, for example, focuses on the "seriousness" of the disease. Of course, the seriousness of the disease is not irrelevant, but if sufficient treatment options for that disease are already available, novel studies are not indispensable.

Boxed text 12.2 shows that both the 46.407 policy and the 46.406 policy also require that assent is asked for from children who are able to provide it. However, this is a general requirement that also applies to studies with minimal risks and burdens. Neither the 46.407 policy nor the 46.406 policy mention that in cases of "higher risk, no direct benefit" studies, the assent of the child is critical; i.e. that "higher risk, no direct benefit" studies with children who are unable to give their assent to participate in the study should not be approved.

12.4.2 National Review

In addition to the above-mentioned criteria, both policies have their own specific characteristics. The main characteristic of the 46.407 policy is that it involves review at a national level: The Secretary of the Department of Health and Human Services (HHS) may approve studies after consulting a panel of experts and

providing a period for public comment. Such a special review procedure seems to offer a clear advantage: It reminds both researchers and review board members of the fact that an exception to an important basic rule is being made. Our only critique is that the procedure may be too complex in its current form. As a consequence, only 17 studies were submitted for this type of review between 1981 and 2005 (Kopelman and Murphy 2004; Ross 2005; Wendler and Varma 2006). Several ethicists and researchers have argued for more transparent and timely review (Kopelman 2004; Rosenfield 2008; Ross 2004).

12.4.3 Regular IRB Review

The 46.406 policy, in contrast, involves review by regular IRBs. "Higher risk, no direct benefit" studies must fulfil two additional selection criteria to be considered for such a relatively relaxed review procedure. These criteria are that (1) the study should not involve more than a minor increase over minimal risk (46.406-a); and (2) the subjects should have the disorder or condition under study (this is part of 46.406-c) and should be (or be likely to become) familiar with the research procedures (46.406-b).

12.4.3.1 A Minor Increase Over Minimal Risk

The criterion of "a minor increase over minimal risk" seems logical: The greater the increase over minimal risk, the stronger the need for a more comprehensive review procedure. However, we believe that the concept of "a minor increase" is too vague to offer a reliable threshold for institutional review. Neither the US National Commission nor any of the scholars who have proposed definitions in the literature have succeeded in making this concept fully clear (Freedman et al. 1993; Wendler and Emanuel 2005). This is not surprising, because defining "a minor increase" as an insignificant increase would make it difficult to distinguish between "a minor increase over minimal risk" and "minimal risk", whereas defining "a minor increase" as a significant increase would raise the question of whether bypassing the more comprehensive review procedure could still be ethically justified.

12.4.3.2 Subjects with the Disorder or Condition Under Study

It may well be that the 46.406 policy was based on the idea that bypassing the more comprehensive national review procedure could be ethically justified because the 46.406 policy only deals with studies that involve subjects with the disorder or condition under study (46.406-b and 46.406-(c). In other words, perhaps the 46.406 policy was based on the idea that whereas the basic level of acceptable risk is minimal risk for healthy children, it is a minor increase over

minimal risk for sick children. However, this would imply that sick children are regarded as requiring a lower level of protection than healthy children. Why would one make such a distinction between sick and healthy children? Below, we will consider and reject the four possible reasons.

Firstly, the distinction between sick and healthy children could be based on the assumption that children with the disease or condition at stake are likely to benefit from the research in the future, whereas other children will not. This may sound logical, but on examination, it is not completely evident: Children who participate in studies that cannot directly benefit them may have grown up, been cured, or may even have died by the time the results reach the clinic. Of course, many studies may directly benefit their subjects, but such "studies with the prospect of direct benefit" form a different category and do not need to meet the requirement of minimal risk and burden.

Secondly, the distinction could be based on the assumption that sick children are categorically more likely to be able to give their assent to participate in a study. Indeed, research suggests that children with cancer report themselves feeling more mature than their peers (Lozowski 1993; Maggiolini et al. 2000). This effect, however, is probably limited to some serious and/or chronic diseases, and disease status clearly is not the main factor of influence: A healthy 14-year-old child will be more capable of deciding whether or not to participate in a study than a sick 3-year-old. Familiarity with the procedures may help children make knowledgeable decisions: A child who has previously experienced a particular procedure may better understand what it means to undergo the procedure again. However, being sick could just as easily make children more vulnerable to the "therapeutic misconception"; that is, they could be more likely to fail to distinguish research from clinical care.

Thirdly, the distinction could be based on the assumption that sick children are categorically more likely to come to embrace their contributions to research on their own diseases. However, there is no empirical evidence supporting this assumption. On the contrary, Wendler has shown that the few data collected so far show essentially no difference in individuals' willingness to participate in research on their own disease compared to research on other diseases (Wendler 2010). He explains this by the fact that people develop numerous allegiances during their lifetimes, and the kind of research that one assumes these individuals will be likely to support depends on which of their allegiances one focuses (Wendler 2010). Children may just as easily identify with children within the same age group, within the same country or with the same disease as someone who is close to them.

Lastly, the distinction could be based on the assumption that research risks or burdens are systematically lower for sick children than for healthy children. However, research risks are increased rather than decreased for sick children compared with healthy children. When taking blood samples, for example, the risk of severe anaemia is higher in an anaemic than a healthy child. The same applies to the research burden: Whether familiarity with a procedure reduces its burden is highly uncertain; it might well be the other way around (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1977).

12.5 Recommendations

In the light of the foregoing analysis, we advise that Europe does not follow the US Federal Regulations completely.

(1) Instead of the fairly nonspecific selection criteria found in the US Federal Regulations, we recommend using selection criteria that are more closely related to the two factors that determine when exceptions to the requirement of minimal risk and burden can be ethically justified. Thus, we propose that "higher risk, no direct benefit" studies may be approved when:

   (a) The potential subjects are able to give their assent to participate in the study; and
   (b) The study can be regarded as exceptionally valuable because:

   (i) The desired data are truly indispensable for improving medical care for children (i.e. no or insufficient treatment, diagnostic or preventive options are available for the disease at stake, and the desired data are likely to make a significant contribution towards developing a new option); and
   (ii) The study design is ideal compared with other possible designs (i.e. the methodology is of excellent quality, and the subjects do not have to face more risks and burdens solely for research purposes than strictly required to obtain the desired data).

(2) A special review procedure emphasises the fact that an exception to an important basic rule is being made; however, the 46.407 review system currently used for that purpose in the US seems too complex. A standing central review board could be a feasible alternative. Compared with the 46.407 system, review by a standing central review board would offer two additional advantages: (1) The procedure would take less time and effort; and (2) a central body of expertise would be developed.
(3) Accurately selecting those "higher risk, no direct benefit" studies that are suitable for a less comprehensive review procedure is very difficult. It seems better to have just one policy.
(4) Some levels of risks and/or burden may be unacceptable even if the study is exceptionally valuable and the subjects are able to give their assent. Consider, for example, studies such as the Phase I healthy volunteer studies advertised in newspapers, involving several weeks in hospital, arterial lines and so on: Would we allow children to miss school for such a long time to undergo these procedures for research purposes? We therefore propose to start a debate on the upper level of acceptable risk. To approach this issue, we recommend that review boards develop and publish (for example, on a dedicated website) written rationales to explain the basis for their judgments to a broader public. Such case decisions could be helpful in identifying the upper level of acceptable risk and could create useful exemplary cases. Focus groups with paediatricians, parents and children may also be helpful.

12.6 Concluding Remarks

If, in Europe, paediatric studies cannot directly benefit the research subjects, the risks and burdens may not be more than minimal. The US Federal Regulations offer two possibilities for approving "higher risk, no direct benefit" studies. We have argued that exceptions to the minimal risk and burden requirement in certain circumstances can indeed be ethically justified. We believe that Europe should adopt a policy that acknowledges this. However, rather than following the US Federal Regulations, we recommend Europe to adopt a policy that is more closely related to the two factors that determine when exceptions to the minimal risk and burden requirement can be ethically justified: The assent of the research subjects and the value of the study.

Regarding the required assent of the research subjects, two issues deserve attention. Firstly, there is the issue that decisions regarding potential exceptions to the requirement of minimal risk and burden have to be made during the review phase, which means that the assessment of whether the potential subjects are able to give their assent must be made on a rather abstract group level. We propose that review boards base this assessment on the general characteristics of the group of children who will be asked to participate in the study (e.g. age, developmental status and familiarity with the study procedures) and on the question of whether it is the risks and/or the burdens that exceed the minimal level. The potential subjects must be expected to be generally capable of understanding the purpose of the study, of understanding the risks and burdens they have to face solely for research purposes, and of making their own decisions based on this knowledge. The second issue is that if our proposal is followed, "higher risk, no direct benefit" studies with children who are not yet able to give their assent can never be conducted, however valuable they may be for future paediatric care. However, we think that this implication is correct, in that children who are not yet able to give their assent to participate in a study deserve greater protection which cannot be overruled by the interests of sick children in the future.

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Part IV
New Developments in Medical Research and Ethical Implications

Chapter 13
A Paradigm Change in Research Ethics

Rieke van der Graaf and Johannes J. M. van Delden

13.1 Introduction

Medical research is widely recognized as important and valuable. Its outcomes might ultimately improve the health and well-being of present and future people. In order to develop socially valuable health knowledge, it is necessary that human beings participate in medical research. At the same time, participation of human beings is not self-evident. Since the Second World War, it has been widely acknowledged that enrolling human beings in clinical trials and observational studies requires ethical justification. Historically, scandals and controversial cases have created a need for justification. However, even when scandals are absent, we need to justify why it is acceptable to use human beings primarily for the sake of third-party interests, such as science and society. Jonas (1969) has notoriously written that:

> We must justify the infringement of a primary inviolability, which needs no justification itself. (Jonas 1969)

An overarching justification of what we owe to research participants is, however, lacking. Some people have formulated negative obligations towards research participants, such as the idea that participants should not be exploited (Emanuel et al. 2000; Miller and Brody 2003), or not used merely as a means (Van der Graaf and Van Delden 2010). There is, however, no universally accepted theory for research ethics which sets out what we owe to human beings in clinical research, including our positive obligations to participants.

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In order to formulate this theory, we first need to reflect on the nature of research participation itself. Until recently, medical research involving human beings has been regarded as a perilous undertaking that is inherently burdensome to participants. Enrolling human beings in clinical trials had to be justified exactly because virtually every clinical trial and observational study imposes risks and burdens on participants that are absent when they do not participate. In some studies, participants might directly benefit, though this is not something which is certain at the start of a trial. The medical treatment or procedure may also be harmful. Furthermore, even if they benefit, they may be exposed to discomforts that are absent both in the regular care for their diseases and in other areas of daily life, such as extra blood draws, magnetic resonance imaging measurements (MRIs) and biopsies.

In this paper, we hypothesize that the current paradigm for research ethics, underlying our positive and negative obligations, is changing. We claim that in the new paradigm, human subjects research is regarded as an "ordinary rather than an extraordinary practice in our society". If our claim is correct, it may influence a future theory of research ethics. This theory may concentrate on the question of how we may encourage people to participate in clinical research rather than on what the best way is to protect them against incremental risks and burdens.

One way of justifying human subject research is focusing on what we owe human beings as a minimum. We will start our paper by briefly discussing the principle of not using people merely as a means and set out what the limitations of such a negative obligation are. Next, we will describe three indications in the literature that point at a paradigm change and discuss the implications of this change for a future theory of research ethics. We will conclude this paper arguing that in the new paradigm, research involving human beings needs to be justified because we have to determine what we owe them, both positively and negatively. There is no longer a need to justify an unjustifiable practice.

13.2 Negative Obligations in Human Subject Research

There are many guiding principles that focus on the question of what we cannot do with human research subjects. One of these principles is the Kantian idea that people must not be used merely as a means. Intuitively, the practice of clinical research itself seems to violate precisely this idea. Participants in clinical research are used as a means for the interests of other patients. Participating in research may involve incremental risks and burdens that cannot be offset against benefits in medical progress. This may imply that people are not only "used as a means" for these purposes, but also "used merely as a means". In general, using people as a means becomes ethically problematic if we also use them "merely" as a means.

In a recent paper on this principle, we have argued that participants are used merely as a means if the conditions of possible consent and end-sharing cannot be met (Van der Graaf and Van Delden 2010). When participants have no sufficient reasons to consent to being enrolled and hence, cannot share the ends of the researchers who use them, they are used merely as a means. People have sufficient

reasons if all stakeholders of a medical trial or study agree on a general level that participation is acceptable both in light of the ethical principles for clinical research (Emanuel et al. 2000) and the extent to which these principles can be met in a specific case. In order to evaluate whether sufficient reasons exist, it should be discussed when it is reasonable to ask people to participate in clinical research. This is precisely what is often done at the level of Research Ethics Committees, which consist of stakeholders of relevant disciplines. These stakeholders have to determine whether a research proposal can be approved, which implies that they evaluate whether it is reasonable to ask potential subjects to consent to participate. The condition of end sharing implies that researchers and the participants have to find an end that both can share. Obviously, participants and researchers may have personal ends. People may participate primarily because they hope to benefit therapeutically, or to gain extra physical attention. Researchers may conduct a clinical trial because they have to meet targets of their department or institution, or because they hope that the results can be published in a high impact factor journal which may be of benefit to their careers. Nothing is wrong with having personal ends. Neither researchers nor participants have to be pure altruists who only participate because they want to contribute to the well-being of others. Only if the personal ends of participants and researchers interfere with the ends that both have to share, are participants used merely as a means if they are enrolled (Van der Graaf and Van Delden 2010).

The principle of not using people merely as a means functions as a threshold for enrolling human beings in clinical research. It clarifies what we "minimally" owe to human subjects. The principle of not using people merely as a means is part of the Kantian categorical imperative that people must not be used merely as a means, but always used as ends in themselves at the same time. Thus far, however, what it means to use research participants as ends in themselves has not been examined. The positive part of the categorical imperative is an open question as regards human subjects research.

Another example of limits to what we can do with research participants is the so-called "Kantian universalizability test", meaning that we ask in every single case whether we reasonably want all physicians to give preference to their patients in a given way (Chiong 2006). A third principle is the idea that we must not exploit participants in clinical research (Emanuel et al. 2000; Miller and Brody 2003). According to the Emanuel framework, all seven principles (scientific validity, social value, informed consent, fair subject selection, respect for enrolled subjects, favourable risk–benefit ratio, and independent review) stem from the idea of non-exploitation. It is not the purpose of this paper to summarize and analyse all these obligations in detail. We hope to have demonstrated that these obligations only justify a part of human subject research. Another limitation of these principles is that they have been formulated within the framework that research with human beings is inherently problematic and hence, needs to be justified by focusing on what we minimally owe to human beings. The new paradigm may influence a theory of research ethics by also focusing on what we positively owe human beings in research.

13.3 Indications for a Paradigm Change

There are at least three indications in the literature for a paradigm change. Firstly, over the past few years, bioethicists seem to argue in favour of a "duty to participate". According to Harris (2005), and later also his co-author Chan and Harris (2009), we have a duty to participate in medical research based on two principles. The first is the principle of fairness, which they also call "the free rider argument":

> If you benefit from an institution or practice, such as the ongoing institution of scientific research, and accept the benefits that derive from that institution, then you have, 'in fairness', a reason to support the existence of that institution or participate in that practice. (Chan and Harris 2009)

According to Harris we cannot be free riders who benefit from the sacrifices of others (Harris 2005). He regards research as a social institution which should be supported for reasons of fairness (Chan and Harris 2009). Harris and Chan also think that the principle of beneficence, also called the duty of rescue, is relevant here (Chan and Harris 2009). According to this principle, we have to support beneficial and life-saving research (Harris 2005; Chan and Harris 2009). Harris argues that:

> Where our actions will, or may probably prevent serious harm, then if we can reasonably (given the balance of risk and burden to ourselves and benefit to others) we clearly should act because to fail to do so is to accept responsibility for the harm that then occurs. (Harris 2005)

Both papers of Harris, however, have been challenged, in particular by Brassington (2007, 2011). Interestingly, Brassington does not so much criticize the duty to participate, but the principles on which Harris bases the duty (2011). Brassington believes that, "supporting research as a means of rescue is a 'prima facie' duty at most" (2011). People may also benefit other people by activities other than research. As regards the fairness argument he argues that:

> Chan and Harris have not established either that those who benefit from an institution without supporting it are free-riders, that free-riding is a problem of fairness, or that fairness is likely to generate an obligation to support research (2011)

His main problem with Harris and Chan is that a "reason" to participate in research does not imply that people also have an "obligation" to participate (2011). Owen Schaefer et al. (2009) are also unconvinced by the free rider argument and the beneficence argument. They argue against the free riding argument that participation "does nothing to relieve the burdens on those who are actually participating in research" (2009). According to Schaefer et al., the beneficence argument is either too demanding or useless. It is too demanding because it implies that as long as society benefits, significant risks to individuals are acceptable. It is useless when a weaker version of the argument is accepted, since it does not explain why people have a duty to participate instead of having another duty that benefits society. Unlike Brassington, however, they have made further attempts to come up with a new argument to justify a duty to participate.

They defend it on the basis of a so-called public goods argument. This argument entails that:

> Individuals have an obligation to participate in biomedical research because the knowledge produced by the system of biomedical research is (…) a public good. (Schaefer et al. 2009)

Medical research generates knowledge that is beneficial to all of us. According to Schaefer et al., there are no indications that our society thinks that this knowledge is unimportant. Therefore, all have a duty to participate. Interestingly, they also state that:

> Participating in research is much less burdensome than contributing to many other public goods; joining the army is more risky and time-consuming than any clinical trial that has been approved by a well-functioning institutional review board. (Schaefer et al. 2009)

They call for a

> […] cultural shift in the moral framework that is brought to participation in research. The standard view of research participation must be changed from one in which participation is supererogatory to one in which individuals need to give a good reason not to participate, (Schaefer et al. 2009)

In sum, although the duty to participate is not unchallenged, there is a tendency among bioethicists to argue in favour of such a duty. Where Hans Jonas, in 1969, was reluctant to enrol other human beings apart from the researchers themselves in clinical research, we are now confronted with the opposite: Non-participation in clinical research has to be justified. This new perspective on participation can be considered to be in line with the paradigm in which participation in research is not primarily regarded as a burden.

Secondly, the Declaration of Helsinki's (world medical association (WMA) 2008) sixth principle that "in medical research on human subjects, the well-being of the individual research subject must take precedence over all other interests" is being contested (Helgesson and Eriksson 2008; Wertheimer 2011). Similar principles can be found in other ethical guidelines in which these principles also often have prominent places. Gert Helgesson and Stefan Eriksson have tried to make sense of this "primacy principle", but have not found a "reasonable interpretation". They propose six interpretations which should be (1) semantically and logically plausible, and (2) not make redundant what is elsewhere determined in the guidelines. The first interpretation is that "only research with a direct positive balance for the research participants, for instance in terms of well-being, should be permitted". This interpretation is rejected since it does not meet requirement 1. Many guidelines also argue for non-beneficial research. According to the second interpretation, Helsinki 6 is another way of saying that the dignity and integrity of people should be respected. However, respect for the dignity and integrity of research participants does not imply that their well-being should also have precedence over research interests. A third interpretation is to regard the primacy principle as equivalent to what is minimally required in treating human beings in research. Since that is also specified in other principles in the guidelines, this

interpretation is redundant. Fourthly, Helsinki 6 can be interpreted as requiring that "the entire system of biomedical research should leave the individual on an expected positive balance". Helgesson and Eriksson think this is implausible, since Helsinki 6 explicitly acknowledges that individual and societal interests do not coincide. A fifth interpretation is that the research participant should have the final say, but this interpretation is redundant due to principles of informed consent in the guidelines. Finally, it may be intended as a main guiding principle. However, it currently fails in this function, since it does not have a meaning "more legible than the principles it helps to interpret". For these reasons, Helgesson and Eriksson have suggested eliminating the primacy principle from ethical guidelines (Helgesson and Eriksson 2008). Wertheimer (2011) has argued that the principle would impede many research proposals if the well-being always had priority. In many trials this is not the case.

Thus far, Helsinki 6 has hardly been questioned in the literature. Apparently, it no longer has a sacred status within research ethics. More importantly, plausible interpretations of this principle seem to be absent. It appears to be explicitly acknowledged that the well-being of human beings in research must sometimes be compromised for societal benefits. This view is in line with a new paradigm in which the burdens to participants are an acceptable part of the research enterprise itself.

Thirdly, some authors suggest that the incremental risks and burdens of research could be considered as part of the game. The burdens become ethically problematic only when they exceed thresholds or become excessive. In this context, some are considering what the threshold for minimal risk or negligible risks is (Wendler 2009), others, what the limits of permissible research risks are (Miller and Joffe 2009). Human subject research is also compared to other practices in life. If we are faced with incremental risks and burdens, the immediate question is to what other practice in society participating in human subject research can be compared. Some have suggested likening participants to voluntary firemen (London 2007), others to donors of living organs who are unrelated to the recipient (Miller and Joffe 2009). The main ethical problem, as these scholars see it, is finding acceptable levels of risk rather than justifying that people are exposed to research risks at all.

If research participation is being regarded as a positive good, then a future theory of research ethics might focus on ways to encourage participation in clinical research rather than to impede it by merely focusing on principles that determine what we minimally owe human subjects. Furthermore, these principles may no longer be regarded as absolute principles that can never be violated, but as side constraints to a practice that is inherently socially valuable. An example of this new consideration can be found in the work of Wertheimer (2011), who has argued under which circumstances exploitation in clinical research can be acceptable. He has pointed at mutually consensual forms of exploitation where the exploitee also benefits, all things considered. Similarly, we have argued that using people merely as a means is not always morally wrong (Van der Graaf and Van Delden 2010). Human beings who participate in clinical research are, to a certain extent, objects or means that are used for the greater good of obtaining scientifically and

socially valuable knowledge. That does however not imply that they are also used "merely" as a means. Moreover, using people merely as a means may not always be morally wrong. An example of this is when the researcher is careless because he or she forgets to deliver an informed consent letter; the researchers may be blamed for the incorrect attitude rather than for acting in a morally unacceptable way, provided that the REC has approved the information letter (Van der Graaf and Van Delden 2010).

13.4 Conclusion

The academic debate on what we owe to human subjects in clinical research is changing. At least among scholars, human subject research seems to be regarded as an ordinary rather than an extraordinary practice in our society. Hence, human subject research does not deserve justification primarily because it is always problematic to enrol human beings in clinical research. Rather, we need to justify human subject research because we have to determine what we owe human beings in research, both in a negative and positive sense. As regards our negative obligations, we have to elaborate to what extent deviation from these obligations is acceptable in a society where clinical research is regarded as an acceptable practice that may involve risks and burdens to participants. Thus far, positive foundations on what we owe to human beings in clinical research have been absent. The observed paradigm change may no longer blind us to positive ideas on what we owe to research participants.

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Chapter 14
Translation of Cancer Molecular Biomarkers: Ethical and Epistemological Issues

Flavio D'Abramo and Cecilia Guastadisegni

14.1 Introduction

Cancer diseases during the last four decades have increased and an epidemic is now present. Compared to the 1970s, the cancer incidence and mortality has doubled. The rising cancer incidence and mortality has many causes: For instance, the estimated life expectancy has increased and, consequently, the degenerative diseases also; the number of world inhabitants has increased and the industries have increased the carcinogenic exposures in an exponential manner.

In order to face problems posed by epidemics such as cancer, international drug agencies since 1992, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have shortened the approval process of drugs for serious or life-threatening diseases (Johnson et al. 2011). To allow the shortened approval process, the criteria utilised in the normal procedure have been replaced by surrogate endpoints: For instance, prolongation of life has been substituted by disease-free survival—also known as the relapse-free period or progression-free survival. In the shortened approval process, pharmaceutical companies have to supply single-arm trials and then confirmatory post-approval trials. In the case that drug endpoints are not confirmed by post-approval trials, or in the case that post-approval trials are not carried on, the regulation allows the drug to be removed from the market.

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The purpose of the accelerated approval regulation is to make drugs more rapidly available to cancer patients where the treatment is directed at prolonging their life or giving them a better life. In this article, we focus on the use of the monoclonal antibody cetuximab for metastatic colorectal cancer (CRC) patients.

Cetuximab was approved within an accelerated process either:

- as a single agent in patients intolerant or unresponsive to the standard chemotherapy (irinotecan- and oxaliplatin-based regimens); or
- in combination with standard chemotherapy for patients refractory to standard chemotherapy.

The first indication has been converted to a regular approval, whereas for the second indication, the approval is still based on the accelerated process run in 2004. Even though the accelerated approval has prompted many criticisms, the approval of targeted drugs for metastatic cancer has been invoked as an "ethical imperative" (Yap et al. 2010).

In this paper, we discuss the inconsistencies of the genetic model of cancer as applied in the case of CRC and the ethical implications relevant to the physician–patient relationship, as well as the fair distribution of limited resources in healthcare.

14.2 Targeted Therapy for a Genetic Model of Colorectal Cancer

Targeted therapy is a term used to describe a new generation of cancer drugs designed to interfere with cellular targets that have a critical role in cell growth and hence, cancer progression. The identification of cellular targets for therapeutic intervention has been achieved by the sequencing of the cancer genome, since cancer is seen as a genetic disease. Cancer DNA sequencing has identified key genes whose mutated proteins are considered a pharmacological target; an example of this kind of genotype-directed approach of targeted cancer care is cetuximab, used in patients with advanced colorectal cancer (Taylor and Ladanyi 2011).

Colorectal cancer samples can be obtained through surgical resection or colonoscopy at various stages of development, from the early benign adenoma to the malignant carcinoma. For this reason, the development of this type of cancer has been studied in depth and can be considered as a prototype for solid tumours. In the 1990s, during early investigations on CRC, it was proposed that the development of a carcinoma is a clonal expansion of one cell which has acquired a growth advantage. This growth advantage has been acquired through a series of mutations of specific genes in the cancer cell. According to the genetic model of cancer development, the progression of cancer from the benign adenoma to the aggressive carcinoma cancer is understood as a multi-step process requiring several genetic mutations. Due to these mutations, there is deregulation regarding the

control of cell proliferation, cell differentiation and cell death (Fearon and Vogelstein 1990).

The strategy of new cancer drugs is to modify the deregulated intracellular pathways of cancer cells by reprogramming the cell circuit and suppressing the acquired growth advantage. The hypothesis that cancer cells would respond to the pharmacological modification of mutated pathways is based on the notion that intracellular pathways mimic electronic integrated circuits. According to this concept, cancer is a derangement of the integrated circuit of the cell and, therefore, similar to electronic circuits, intracellular pathways should respond to a precisely defined set of rules. Anti-cancer drugs can then be used to modify the mutated pathways (Hanahan and Weinberg 2000).

The model targeted agent for metastatic colorectal cancer is cetuximab, a monoclonal antibody that binds specifically to the extracellular portion of the epidermal growth factor receptor (EGFR). The EGFR is part of a subclass of receptors which transmit growth stimulatory signals across the plasma membrane, and cetuximab competitively blocks the binding of specific ligands[1] to the EGFR receptors. The propagation of the EGFR signal is transmitted through the activation of three parallel intracellular pathways. The treatment of tumour cells in vitro with anti-EGFR antibodies rapidly inhibits the downstream signals and, as a consequence, blocks the proliferation of the tumour cells.

However, the positive in vitro results were not achieved in the clinical setting (Gschwind et al. 2004). Clinical studies in patients with metastatic colon cancer showed that only 10–15% of patients benefited from anti-EGFR targeted therapy, while the rest of the patients receive cetuximab without any advantage, adding severe toxicity (skin reactions, diarrhoea and infusion-related reactions) and wasting economic resources (Bardelli and Siena 2010). In light of the difference between in vitro results and clinical research, it was hypothesized that mutations in the KRAS gene might be the cause for patients' unresponsiveness. This is because experiments indicate that when the KRAS protein is mutated, the proliferation signal is activated regardless of the activation of EGFR receptors by the specific ligands (Van Houdt et al. 2010).

However, the use of KRAS gene mutations test in the clinical setting has shown that the predictive power is limited. Therefore, it has been recently hypothesized that only tumours harbouring no mutations in all the three parallel intracellular EGFR pathways might be the ones more likely to respond to cetuximab. New additional biomarkers are under investigation (Sartore-Bianchi et al. 2010). The use of molecular biomarkers is the procedural prototype for the model of personalised cancer treatment, with the aim of administering a drug tailored to the genetic make-up of the individual tumour. These cancer molecular biomarkers are identified by genotyping the different tumour specimens. This model of

[1] Signal triggering molecule, binding to a target receptor.

personalised cancer treatment is rooted in the view that cancer cells follow a defined set of rules and that each tumour can be suppressed by acting on its own pathways (Hanahan and Weinberg 2000).

14.3 New Anti-Cancer Drugs and Molecular Biomarkers

The approval of the anti-EGFR drug cetuximab represents a case where the biological hypothesis and the preclinical studies played a major role. In 2004, both the FDA and EMA approved cetuximab to treat patients with metastatic CRC (Yap et al. 2010). The approval was granted under an accelerated protocol for serious and life-threatening diseases, with a duty to report post-marketing phase II and III clinical studies to demonstrate the clinical benefit of the approved anti-EGFR drug. Small clinical studies demonstrated that patients receiving cetuximab had a very small clinical benefit, as the addition of cetuximab to the standard chemotherapy prolonged the relapsing period by only 2.6 months. This restricted activity of cetuximab was evident also in larger phase III studies, where the patients treated with cetuximab had a comparable survival time of those patients not receiving the targeted therapy (Vincenzi et al. 2010).

Although the survival benefit for patients treated with anti-EGFR drugs can be measured in weeks, the increase in the cost of cancer care has exceeded that of total health care. The cost of an eight-week course of standard chemotherapy for metastatic CRC patients is 10,000 dollars whereas adding cetuximab to the standard treatment increases the cost to 30,000 dollars (Schrag 2004). The cancer epidemic has shadowed the great societal cost of such treatments, as these staggering costs of cancer drugs have opened a great debate on the allocation of health-care resources. Clinical oncologists play a pivotal role in treatment decisions and, although they may consider these new therapies not to be a "good value" for patients, nevertheless, they believe that cost should not limit a patient's access to effective treatment (Nadler et al. 2006).

As manufacturers are under increasing pressure to demonstrate the high clinical value of new costly therapeutics, the use of biomarkers to target prospective respondent cancer patients or to exclude those with a low probability of response is a powerful method to boost efficacy and reduce the wastage of resources (Woodcock 2009). This "selection principle" has been trying to be implemented through the use of molecular biomarkers in order to achieve personalised cancer treatment. In order to prevent unnecessary treatments, the EMA in 2008 and the FDA in 2009 applied restrictions for the use of cetuximab; Under the economic pressure of wasting health-care resources, the drug agencies limited the use of anti-EGFR drugs to metastatic CRC patients with no mutations in the KRAS gene (Allegra et al. 2009). After the restrictions applied to cetuximab, a second fully human monoclonal antibody against EGFR (panitumumab) has been approved by the EMA in an unprecedented regulatory decision which was driven by the use of a biomarker. This opened a new era in

biomarker-driven oncology (Gravalos et al. 2009). The results of phase II and phase III clinical trials of anti-EGFR drugs were further analysed and the metastatic CRC patients were stratified according to the presence of mutations in the KRAS gene. Patients with no KRAS mutations receiving cetuximab and standard chemotherapy had a significant gain of relapsing-free period of 1.2 months, which did not translate into a gain in survival (Van Cutsem et al. 2009). The results of a second clinical trial showed a similar gain in relapsing-free time of 1.1 months in patients with no KRAS mutations who received the standard chemotherapy with cetuximab, although no survival gain was achieved (Bokemeyer et al. 2011). The anti-EGFR restriction is applied, although KRAS has a very limited predictive power. The results of current research regarding the clinical benefit of patients with no KRAS mutations are not very dissimilar to that of the entire population of metastatic CRC patients. The use of the KRAS biomarker for predicting respondent CRC patients is stirring a high level of uncertainty. This uncertainty, in turn, calls for a renewed appraisal of the doctor–patient relationship.

14.4 Doctor–Patient Relationship and Shared Decision-Making

Nowadays, medical decisions are supposed to be the result of an objective, technical, impersonal clinical process and not so much a consequence of subjective intuition based upon accumulated personal experience (Barona 2006). The traditional structure of health-care gives control to doctors on the basis of their professional authority, which should be built on an evidence-based approach. However, the practice of health professionals is often mediated by practice-based evidence, a characteristic that confers professional authority to physicians. Nevertheless, highly complex cases, such as the treatment of metastatic CRC with anti-EGFR drugs, which show negligible survival advantage, are characterized by many social, psychological, medical, and economic variables. Each of these issues is tacitly or explicitly embedded in the decision-making process. Within these complex and sensitive cases of metastatic CRC, the doctor's authority seems to be a major obstacle.

The approaches used in the patient–doctor relationship can be grouped into two models:

- the agency model; and
- the shared decision-making model (SDM).

The "agency model", deriving from economics, is the one most applied in health-care. In this model, a principal, in this case the patient, delegates authority to an agent, the doctor, to take action. The agency theory reflects a situation of conflicting goals between the physicians and the patients, where often the doctors

have to serve not only the benefit of the patients, but also the interests of third parties, i.e. the pharmaceutical industry (Gafni and Charles 2009). Consequently, knowledge coming from trials, systematic reviews and meta-analyses does not seem to fit easily with the practices of physicians (Rapley and May 2009). Knowledge often coming from scientific journals is then overlooked or considered as "inappropriate"—e.g. less information for the best decision. Informed consent in clinical practice has been influenced by an interpretation of informed decision-making as a legal obligation of full disclosure. The compulsoriness in disclosing all the information is opposed to an ethical approach toward a mutual decision in which the knowledge produced by researchers should help the patient and the doctor in taking the appropriate decision together.

The shared decision-making model states that an increase of available information improves the quality of decision-making. The SDM approach, where alternatives available to face the disease are taken into consideration, describes a situation of partnership which is built on trust and on a positive patient–doctor relationship. In this approach, both patients and physicians interact to describe their treatment preferences while trying to build a consensus. Several criteria should be incorporated in SDM, such as communicating alternatives, pros and cons of the alternatives, and uncertainties associated with the decision. Furthermore, an assessment of the patient's understanding should be considered. In contrast to the SDM approach, physicians and surgeons frequently make decisions without discussing the intervention with the patients or seeking their involvement. Even if the need to share all the variables of the decision-making is often invoked, many approaches justify the importance of reducing the quantity of information available to the oncologists and, therefore, to the patients. Wegwart et al. (2010), for instance, hypothesize that when more information is available, the decision-making quality worsens. Decision-making in clinical practice may fall short of the basic level of patient involvement even in routine decisions (Braddock et al. 1999).

14.5 Ethical Implications of Genetic Information for Decision-Making in Metastatic Colon Cancer

Despite great advancements in understanding cancer pathways and great diagnostic improvements which confer huge authority to oncologists, we hold the view that the actual health-care systems are not interested in knowledgeable patients able to make real shared decisions. On the contrary, we hold that informed patients would be able to demand better care, and informed doctors would be able to propose alternatives among which "no intervention" should be included. The "no intervention" option is rarely proposed by oncologists to metastatic CRC patients.

Following the shared decision-making approach, doctors should take into account the great uncertainty of patient responsiveness to anti-EGFR drugs and the limited benefit in terms of progression-free survival. Furthermore, the awareness

of the limits of cetuximab should be communicated by the doctor to the patient. After showing cetuximab's disadvantages—including the fact that survival might not increase at all, that the relapsing free period will increase at a maximum of 1.2 months, and the related side-effects, such as a severe skin rash—the doctor should propose the option of not being treated with these drugs and discuss other options with the patient. The disclosure of controversial and uncertain points of the anti-EGFR treatment can be the source through which the patients can achieve autonomy in their choices (Rapley and May 2009). Autonomy, in its positive conception, can be considered within an approach in which the scientists, doctors and researchers make efforts to help people to understand the information, which is based on biomarker tests and research on the effectiveness of anti-EGFR drugs. Subsequently, scientists help the realisation of the patients' preferences based on their own values and beliefs (see also Bredenoord and Van Delden, Chap. 11 in this book).

On the contrary, if all the information regarding cetuximab is not disclosed, the use of a KRAS biomarker will create a false hope in both the patient and the doctor, as even the patients with no mutations in the KRAS gene have a negligible increase of relapsing time. The hope is that by increasing the number of biomarkers, only the responding patients can be identified, and the treatment of cetuximab could be more successful (Bardelli and Siena 2010).

The possibility of the SDM approach is questioned if we suppose that the decision-making quality worsens with the increase of information. Nowadays, doctors are rarely able to manage such a delicate communication. To achieve the right communication with cancer patients, especially metastatic cancer patients, is just as much of a skill as performing an operation (Gawande 2010). Several constraints, such as the inadequate teaching about decision-making in communication skills or the lack of time in the health-care organization, make it difficult to implement SDM in an acceptable way (Towle and Godolphine 2009). The complexity of medical information regarding metastatic colon cancer, on the one hand, and the above-mentioned obstacles to the implementation of SDM, on the other hand, provides significant ethically relevant challenges on the level of the doctor–patient encounter. As we will see, this problematic will be complemented by the challenge of fair allocation of limited resources.

14.6 Ethics of the Allocation of Resources

The ethical justification for the use of costly therapeutics, such as cetuximab, is exceptional due to the unique and incomparable value of the end-of-life period. Starling et al. (2007), for instance, sustained that the absolute time of life-saved for patients with a poor prognosis is likely to be short. In that case, we have to embrace the "rule of rescue" for which the last days of life have to be evaluated more preciously than others.

In our case, such a compassionate approach creates two problems:

- The doctor who prescribes cetuximab to help metastatic colorectal cancer patients not responding to standard chemotherapy will ignore the scientific evidence showing the fact that cetuximab is not effective in 85% of the patients, and that the best-case scenario will consist of the increase of 1.2 months (means) of the relapse-free period; and
- The use of cetuximab increases health-care costs, creating serious issues in the health-care management of resources as our health-care systems have limited resources, and a charitable approach diverts funding that might instead be directed to prevent cancer or to develop less costly and more effective alternatives.

As health-care systems are more and more unable to support the increasing expenses, physicians are requested to consider the economic consequences of their decisions with a view to optimize the use of scarce health-care resources allocated to the population. It is possible that in a circumstance of metastatic cancer with poor prognosis, the oncologist may prescribe anti-EGFR drugs on compassionate grounds and often on an "off-label" basis. This means that a doctor embracing the charitable approach might not take into consideration either the KRAS status, or the fact that cetuximab's endpoints (progression-free survival, overall survival and quality of life) are limited. However, this often called "compassionate" drug provision of aggressive medical intervention for metastatic cancer patients has meant a shortening or worsening of the last months of life for many patients, who too often die while taking drugs producing severe toxic effects (Gawande 2010). Up until doctors tell patients that there is nothing more that can be done for them, patients remain hopeful in the desire of extending the remainder of their lives. The anti-EGFR treatment represents an option to be used carefully, as the respondent patients are few, and because those responding will gain limited benefit in terms of overall survival when compared to patients receiving best supportive care only (Van Cutsem et al. 2007). Cetuximab belongs to a class of drugs that cannot heal cancer patients; at best, it can retard the worsening of their health. Therefore, and in light of the enormous financial costs, a sensible action should consist of considering alternative paths, such as best supportive care or palliative care.

14.7 Best Supportive Care

Best supportive care represents a less costly option which does not imply toxicity, such as that produced by anti-EGFR treatments (Joshi et al. 2010). Few voices coming from the oncologist community have highlighted the ethical dilemmas faced during the use of the targeted therapy for metastatic colorectal cancer patients. Fojo and Grady (2009) pointed out that the use of anti-EGFR drugs raises some questions regarding the concept of "benefit" in end-stage cancer cases. They criticised the minimum amount of benefit in order to adopt a therapy as a new standard—in the case

of cetuximab, the benefit is 1.2 months of progression-free survival. They also questioned the fact that the quality of life of that 1.2 months is often overlooked, and the fact that the cost of anti-EGFR drugs is not taken in consideration.

An innovative article by Temel et al. (2010) highlighted that integration of palliative care with standard oncologic care—anti-EGFR drugs included—in patients with metastatic non-small-cell lung cancer extended their survival by approximately two months, and showed clinically meaningful improvements in quality of life and mood—depression and anxiety. It was also shown in the study by Temel and colleagues that the early integration of palliative care led towards less aggressive end-of-life care, including reduced chemotherapy. Basically, the early introduction of palliative care may serve to mitigate unnecessary and tough personal and societal costs.

Even if the extension of the cancer patients' survival is desirable and the aim of curing cancer patients is good, neither the cure nor its commercialization can be an imperative or a compulsory choice, as held by Yap et al. (2010). Medical and scientific progress is desirable and, on the whole, beneficial, but it is not morally imperative for those reasons (Callahan 1976).

The current health-care systems strongly induces therapeutic intervention over detailed and prolonged discussion. Even if the use of anti-EGFR therapeutics and the KRAS biomarker for metastatic colorectal cancer was approved by the EMA and the FDA, the management of colorectal cancer patients with metastasis should be mainly palliative, and patients should be supported in facing such complex physical, psychological, social, and spiritual consequences of the disease (Peppercorn et al. 2011).

14.8 Conclusion

Our analysis indicates that the genetic model of cancer has intrinsic limits which are relevant for treatment decision-making in clinical practice. Moreover, the low predictive power of genetic mutations represents an open issue which is also relevant in other parts of medical practice (see Bredenoord and Van Delden, Chap. 11 in this book). Instead of focusing further on a purely genetic model of cancer, the concept of epigenetics seems to better address the causal connections among external dynamics, such as diet and life style, the endocrine system and what happens at a cellular and genetic level (Gilbert and Epel 2009; Vogelstein and Kinzler 2004). An example of this is the methylation of tumour-suppressor genes, which may explain the increased prevalence of sporadic tumours with age (Fraga and Esteller 2007; Issa et al. 1994).

Given the epistemological uncertainty regarding the development of cancer, the ethical challenges described we hold the view that a debate on how to rebuild the health-care systems in order to face the cancer epidemic should be developed. Such a debate could be put together within a multi-disciplinary context, analysing the contemporary practices utilised for metastatic cancer patients and the

implications for society in allocating a huge amount of resources to use often ineffective drugs such as cetuximab.

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Chapter 15
Rethinking the Ethics of Human Biomedical Non-Interventional Research

Kristi Lõuk

15.1 Introduction

Biomedical ethics covers different interconnected domains: clinical ethics, public health ethics and research ethics. The additional information derived from research ethics enables the first two to develop. Human biomedical research covers the different fields of clinical research and public health research. In most cases, human research is meant to signify clinical research. The current article focuses on human biomedical research.

There is a myriad of guidance materials on ethical conduct in human biomedical research. It is known that research ethics were born in scandal (Levine 1988), for example, the Nazi doctors, the Tuskegee Syphilis Study, the Jewish Chronic Disease Hospital Study, the Willowbrook hepatitis study, the Moore case, and the Gelsinger case. It has been remarked that "born in scandal" is one of the flaws of the guidance (Emanuel et al. 2008). The other flaws are that "regulatory guidance tends not to examine the overall ethics of research, but to have a specific practical purpose", that "existing guidance is neither comprehensive nor systematic" and that "existing guidance seems to be mistaken on several important issues" (Emanuel et al. 2008).

Although there seems to be a consensus that research on personal data and/or biological material differs from other types of research, there is no agreement on how these differences should be regulated. This also means that in addition to physicians-investigators, researchers have an important role in respecting the

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autonomy and privacy of the research subject, and that they also need to follow the principles of human subject research. Solutions that have been proposed (e.g. the acceptance of broad consent) have been criticized as representing biobank exceptionalism,[1] which is not justified, or leads to a slippery slope.

The present work discusses whether the distinction between interventional and non-interventional types of human biomedical research could be a criterion based on which the difference is justifiable, and whether it could form the basis for different solutions in regulatory frameworks.

15.2 Intervention as a Criterion

The distinction between interventional and non-interventional research is easy to make at a descriptive level. Interventional research means that for research purposes, direct physical intervention takes place, for example, by ingesting a substance under study, undergoing procedures, different diagnostics, or preventive or therapeutic interventions (Lõuk 2010). This means that the presence of the research subject is needed, as well as his or her active[2] participation. In the current volume, the article by Anna E. Westra and Jan M. Wit, (Chap. 12), is a fine example of the challenges of interventional research. In order to avoid exploitation and ensure that research is ethical, the participants' voluntary decision to participate is required to protect their autonomy, integrity and dignity. In most cases, this decision is expressed by signing the informed consent form, also classified as explicit informed consent, which covers all the requirements deriving from the Declaration of Helsinki (World Medical Association 2008), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2006) ''Guideline for Good Clinical Practice'' (ICH GCP guidelines) and, depending on the country, funders and researchers, the Common Rule (Department of Health and Human Services, National Institutes of Health, and the Office of Human Research Protections (2005)) or the Council of Europe Additional Protocol (2005).

Another important characteristic is that the physicians/investigators play a key role besides the participants/subjects in the case of interventional research. Non-interventional research means that research takes place on personal data or human biological material which has already been collected, e.g. registries, repositories, electronic health record databases, and collections for future purposes: biobanks and biobank networks. Compared to interventional research, non-interventional research includes minimal physical risk, if any at all, and the

[1] Biobank exceptionalism is a view that biobank research is so special that it requires different moral and legal standards (either more stringent or more lax, often the latter).

[2] It has also been argued that the research participation can be seen as passive (see Wendler 2011).

presence of the research subject and his or her active participation are not required. The main harm is informational, and there are risks to privacy, confidentiality and integrity. Similarly to any type of human subject research, non-interventional research also requires the protection of autonomy, integrity and dignity, as well as the avoidance of exploitation. It has been pointed out that as the research takes place far from the person on whose data or sample it is conducted, it is impossible to have meaningful control over one's data and sample. The author considers genetics research and genomics research non-interventional. However, when one takes into account the issue of the feedback of individual genetic data to research participants, discussed in the article by Annelien L. Bredenoord and Johannes J. M. van Delden in this volume (Chap. 11), this presumes communication and interaction, possibly even constituting an intrusion of privacy, and these activities are interventional. The author would not classify that as research, as these activities are performed because of the post-research obligation, not due to the nature of non-interventional research.

Intervention is a criterion that is used in the much criticized regulatory guidance of research ethics. At the European level, the concept is at the core of the Council of Europe (CoE) documents: The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (1997) (Oviedo Convention), the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research (2005) (Additional Protocol), and the Recommendation Rec2006(4) of the Committee of Ministers to member states on research on biological materials of human origin (2006) (Recommendation). The Additional Protocol states:

> For the purposes of this Protocol, the term "intervention" includes: physical intervention, and any other intervention in so far as it involves a risk to the psychological health of the person concerned. (Article 2)

Looking at the definition used in the protocol, it seems that the concept of "psychological health" plays a crucial role, as questionnaires, interviews and observational research taking place in the context of a biomedical research protocol constitute interventions when they involve a risk to psychological health, although slight and temporary emotional distress would not be regarded as psychological harm. At the same time, the protocol does not cover all human research, for example, interventions which have taken place with the aim of collecting biological material for future purposes or research on tissue samples or data that has already been collected, which was the main reason for drafting the recommendation.

The U.S. federal regulation known as the Common Rule states that a

> Human Subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. Intervention includes both physical procedures by which data is gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behaviour that occurs in a

> context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (45CRF46).

Comparing these regulatory documents, it is clear that there is a difference in how intervention is defined. This raises the question whether it matters how intervention is understood and whether it may even lead to different outcomes in what is protected and what is not. Where the Common Rule discusses interaction, the additional protocol mentions questionnaires, interviews and risks to psychological health. This leads to the question whether observational research is covered by these instruments or not. In the case of de-identified data, according to the Common Rule, it is not, whereas according to the additional protocol, even observational research could pose a threat to psychological health and is, therefore, classified as interventional.

The difference seems to be whether observational research is covered by these instruments or not, and whether the data are in an identifiable form and constitute a possible risk of harm to psychological health or not.

If questionnaires and interviews are conducted in a non-identifiable way, they may cause slight distress, but not harm, since slight and temporary distress is not regarded as psychological harm. Another difference concerns personal, identifiable data. As mentioned earlier, the Additional Protocol does not address the issue of previously collected data or the use of samples collected for research purposes not yet known.

Although intervention is defined differently, in most cases it is understood in similar ways. The main factors seem to be the possibility of "psychological harm" and the storage of data in an identifiable or non-identifiable form. Next we shall see how similar or dissimilar are the risks that interventional or non-interventional research entails.

15.3 Difference in Risks

There has been considerable debate about whether research on personal data and biological samples involves different kinds of risks, and whether it is lower or higher compared to interventional research, for example, the physical risk of harm in the case of randomized clinical trials. The important characteristics of interventional research are physical intervention and physical risk of harm. The latter means bodily harm and injuries, pain and suffering, and all the physical harm that can occur during bodily intervention. At this stage, it is possible to inform the research subject of these risks and get his or her informed consent. Other examples in addition to the randomized clinical trials (RCTs) already mentioned may be other types of biomedical research (diagnostic, preventive, therapeutic

intervention)—physical load under certain conditions, enduring a low frequency magnetic field, etc.

In the case of non-interventional research, research on personal data in databanks or biological samples in repositories, it is possible to identify different types of harm. Nõmper (2005) has identified three types of harm: physical, psychological and informational. The physical risk could occur, if at all, when the sample is being taken. The psychological risks involve the possibility of submitting and finding out more information than intended (for example, information that would be of relevance also to relatives and family members, who themselves have not given their data or sample for storage for research purposes) and possible research uses which might offend the person. It has been pointed out that these risks can be dealt with by giving information about the possible uses of the database/repository, which would give the people the possibility to decide if they want to participate under these conditions. The possibility of selective opt-out has been recommended as well.

Informational risk is a possible negative outcome of a breach of confidentiality. Such a disclosure may inflict psychological harm, but, according to Nõmper, the main reason to protect research subjects from informational risks is that once the information has been disclosed, it can be used against the person and also against the community. This paper acknowledges that there are specific issues of interventional and non-interventional research at the community level, but a comparative account of these issues is beyond the scope of this paper. Hansson (2005) has argued that the solution lies in social and political measures. In order to have public trust, transparent policy is needed. The ethical review board also has a crucial role here, as they have the responsibility for setting up the requirements for secure handling of the data (including policies about coding, etc.). In order to deal with the concern about third party access, this could be prohibited at the level of national law, so that the ethical concerns about possible misuse by a third party are addressed by social and political measures. These measures should prevent discriminatory practices, and it is the responsibility of the governors of the databank/repository to guarantee that the data will be used in a proper manner and not misused. It is evident that not only is it important that the conduct of researcher/investigator is proper, but also that other measures should be taken as well, such as the establishment of institutions that protect the data sources (e.g. ethical review boards, data protection agencies).

Corrigan and Petersen (2008) have pointed out, based on research ethics guidelines, that "risks in large scale prospective research of the kind associated with biobanks have been viewed as 'minor' compared to those categorized as 'major'" (e.g. serious risk of physical harm). The reason for this, according to them, is that large-scale prospective cohort studies are seen predominantly as observational studies, with interventions limited to surveys and the collection of biological material, where not much harm is expected. When this type of research is compared to classical clinical, interventional research (e.g. clinical trials), it is seen as having fewer risks. However, it is debatable whether the potential breach in privacy constitutes a lesser or higher risk than ingesting a substance under study. Pragmatic rather than ethical arguments have also been used: That the risks are

low and the potential is high, for example, and that this is sufficient to lower the requirements for this type of research. Hansson and Levine (2003) have also pointed out that, contrary to clinical research, the risk for the person is considered to be low. The argument of lower risks has been called biobank exceptionalism, and there have been claims that this type of exceptionalism[3] is not valid. The author agrees partly with the conclusion, since the risks are not lower, but different, posing different threats and requiring different ways to handle them. Whether the term "biobank exceptionalism" is justified on the grounds of lower risk or not lies beyond the scope of this paper. Several scholars (e.g. Takala 2007) have also pointed out the possible threat that relaxing the rules for biobank research would cause a slippery slope for others, because genetic information is not different from other medical information and the justification for the rules is the same. The latter raises the question of what is the goal of research ethics and research regulations. Is it that the justification for the rules is the same, or that the main aim and value—to protect the person—is the same? The author of the paper considers it important to focus on the main aim: to protect the research subjects and the community. If we agree that the outcome is important—despite differences in research, the subjects and community should be protected—then the protection is dependent on the risks and the ways of handling these risks. The main premise for Takala was that research on genetic databases should be subject to the same regulations as all other clinical, interventional research. However, following the intervention criteria, there is reason to argue that non-interventional research (e.g. research on databases and human biological samples) should not be classified as clinical, as the purpose of the research is not directly related to clinical care and takes place in a non-clinical setting (e.g. research laboratory) and, therefore, should not be subject to the same regulations. The question is whether non-interventional research could be classified as clinical, which is an important consideration because it sets the limits of the types of framework and regulations that apply.

We have found that the risks are different and not necessarily lower in the case of non-interventional research, but the differences do not provide sufficient normative grounds for the interventional/non-interventional distinction. In order to find a ground for that, we must turn to the concept of the role of the investigators elaborated on recently by David Wendler.

15.4 The Role of the Investigators

Wendler (2011) points out that clinical research is considered to be ethically problematic and subject to extensive regulation. He continues by stating that although this view is frequently endorsed, there has been almost no systematic

[3] It is important to note that exceptionalism is discussed in the context of research, for example, research merits stringent regulation even if it is no riskier than many other activities (see, for example, Wilson and Hunter 2010 and Hansson 2011).

evaluation why clinical research might be ethically problematic. According to his view, commentators who consider this question tend to assume that clinical research is ethically problematic because it exposes some individuals to risk for the benefit of others. Wendler compares clinical research with two other activities that expose some individuals to risk for the benefit of others, and shows that this comparison highlights an aspect of clinical research which has received relatively little attention—the active role investigators play. He argues that this aspect explains much of the ethical concern expressed about regulating clinical research.

In the following, Wendler's argumentation is briefly introduced and, subsequently, it will be tested whether it could have an impact on the interventional/non-interventional distinction.

Wendler claims that the ethical analysis is dependent on whether researchers interact with subjects directly or not. A specific aspect of clinical research is the way in which risks are presented to the participants. Clinical research typically involves direct interaction between investigators and subjects, as well as investigators actively performing procedures on subjects that pose risks; for example, inserting needles into subjects' backs to obtain spinal fluid for research purposes, dropping potentially toxic substances into subjects' eyes, or giving subjects experimental medications and performing research scans and biopsies on subjects. The examples Wendler uses could be classified as interventional. It is important to note that the investigators have organised the activity and invited individuals to participate and, at the same time, the actions of the researchers (e.g. needles and experimental medications) are the source of the risks and harm subjects face. Wendler, therefore, shows that "the very design of clinical research trials involves the investigators as the proximate cause of harm experienced by the subjects", even though clinical researchers take steps to minimize the risks of clinical research (e.g. monitor side effects, use low doses).

According to Wendler, the ethical concern posed by clinical research may be traced to the fact that investigators do not simply organise and invite individuals to participate in an activity that poses risk for the benefit of others. Investigators actively perform procedures on subjects that pose risks to them for the benefit of others. The examples that Wendler uses here could be classified as non-interventional (although he sees these as a different form of clinical research): Research on medical records or using previously obtained biological samples. As was stated earlier, this type of research poses different risks, not physical, but informational—risks to confidentiality, social status and insurability in Wendler's terms. One should not draw the conclusion from this that non-interventional research is, by its nature, less problematic. It is important to realise that the nature of research, the role of the investigators and the related risks are different, and the difference, as such, has not received the attention it needs in regulating human subject research. One important difference is the role of the investigators. In the context of non-interventional research, the main concern is third party access to (research) information and the possible threat that this will be used to harm

subjects. A proposed solution lies in trustworthy institutions[4] and for that, a democratic public sphere is needed.

It can be seen that on the level of risks, the two types of research have considerable similarities. A specific aspect of non-interventional research is that it does not involve "investigators as the proximate cause of subject harm", as the investigators are not performing procedures on the subjects, and the concern, according to Wendler, is outside, third party access to research information which can lead to informational harm.

Is it possible to classify research on previously obtained biological samples or medical records as non-interventional? Wendler states that "the investigators conducting such research are not interacting[5] with subjects". The aspect of the lack of interaction is the reason why Wendler suggests that non-interventional research does not raise ethical concerns at the same level as other types of research, because investigators are not directly exposing subjects to risks.

According to Wendler, in order to appreciate the presumed normative difference, one has to consider the process by which the participants face risks, and the roles that the organisers play in these processes. The fact that the investigator has the causal role with respect to harm in interventional clinical research is of normative relevance, and this normative significance is beyond the significance of the harm itself.

15.5 Non-Interventional Biomedical Research and the Role of the Investigators

According to Wendler, the causal role affects the relationship investigators have with subjects, and also the level of responsibility investigators and researchers have for the risks subjects face and the different types of harm they experience. Considering interventional research and physical harm, it has been claimed that it is possible to inform the person about these risks and to obtain his or her informed consent. With regard to non-interventional research, this poses informational risks and, through that, also economic risks, psychological risks, etc., and these risks often occur in cases in which the investigator might not have contact with the subject at all. This could be the case in research on personal data or biological samples that have been obtained previously. This could also be the case when the data and samples have been obtained from a database or repository where they have been stored for future purposes. Direct contact between the investigator and the subject takes place when the sample is obtained and also if additional

[4] This notion was first introduced by Baroness Onora O'Neill in her article in 2001.

[5] This lack of interaction should be viewed as a type of non-interventional research, which could be seen in the European context as non-interventional due to the lack of psychological harm. Psychological harm here should be understood as it is explained in the explanatory report of the Additional Protocol.

information is requested, but it is possible to get information from other registries or databases, and in these cases, there is no direct contact. Considering samples and data, the question seems to be in what form are they accessible to the investigators. If the investigators receive the information in a coded or non-identifiable way, then it is hard to see that the investigator would cause harm to the subject simply due to the fact that research takes place. Possible harm to communities should be avoided, but elaborating on the measures is beyond the scope of this paper. While recognizing the role and responsibility of the investigator, it is important to clarify the distinction between the role of investigators and researchers, on the one hand, and that of data collectors and other people participating in the process (e.g. by coding), on the other, as many of the risks discussed could occur due to data handling and not due to the causal role of the investigators.

15.6 Conclusion

The present work discusses whether the distinction between interventional and non-interventional types of human biomedical research could be a criterion based on which the difference is justifiable, and whether it could form the basis for different solutions in regulatory frameworks. Current regulatory approaches and the dissimilarity of risks are also elaborated on.

Based on Wendler, it is possible to argue that a normative ground for making the distinction between interventional and non-interventional research, namely the active role of the investigators, exists. From the analysis based on the difference in risks and the causal role in harm the investigators play, it is evident that the time for "one size fits all" solutions has passed. The distinction between interventional and non-interventional research enables us to find new, more suitable and more contextualized solutions in human biomedical research regarding the protection of research subjects, and their data and/or samples.

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