FEDERAL DEMOCRATICREPUBLIC OFETHIOPIA

MINISTRY OFHEALTH

NATIONAL DRUG INFORMATION SERVICE TRAININGCOURSE FOR PHARMACISTS

PARTICIPANT'SMANUAL

April 2018

APPROVAL STATEMENT OF THE MINISTRY

The Federal Ministry of health of Ethiopia has been working towards standardaization and institutionalization of In-servise Trainings (ISTs) at national level. As part of this initiative the ministry developed a national in-service training directive and implementation guide to implement trainings in a well standardized manner. The directive requiers all in-service training materials fulfill the standards set in the implementation guide to ensure the quality of in-service training materials.

Accordingly, the ministry reviews and approves existing training materials based on the IST standardization checklist annexed on the implementation guide.

As per the national IST quality control process, this national drug information service training courses for pharmacists training package has been reviewed using standardization review checklist and approved by the ministry in April 2018.

Dr Getachew Tollera
Human Resource Development Directoriate Director
Federal Ministry of Health

Foreword

The Federal Ministry of Health (FMOH) has been coordinating sector wide reforms that aim to improve equity and quality of health services. It is widely known that; the sector is growing in line the overall growth and transformation plan of the country and the sector is being guided by the health sector transformation plan (HSTP). As part of these efforts, to achieve the targets set, the sector identified information revolution as one of the transformational agendas. In the meantime, Appropriate and timely use of health and health-related information is an essential element in the process of transforming the health sector.

Access to unbiased and up-to-date drug information is one of the key strategies to promote the rational use of medicines thereby provide quality patient care. This requires establishing and operating drug information service (DIS) at health facilities. In this regard, efforts have been made by FMHACA,PFSA,and School of Pharmacy (Addis Ababa University), in collaboration with development partners. As a result, many health facilities were able to establish and provide DIS, though the level of functionality varies. In addition to responding to drug information queries, drug information centers can carry out many other related activities that can ultimately contribute to the quality of healthcare in the facility.

Thus, the development of this training manual is an important step to address knowledge, skill and attitude gaps identified to provide accurate, up-to-date, timely, unbiased, well referenced, and critically evaluated DIS by pharmacists to the health care professionals, patients/caregivers, and the public.

I would like to take this opportunity to thank all who participated in the design and development of this training manual. I would also like to encourage users of the training manual to send their comments regarding the manual to the Ministry via website: http://www.moh.gov.et or PO. Box 1234, Addis Ababa, Ethiopia.

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Director, Pharmaceuticals and Medical Equipment Management Directorate

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Acronyms

ADR/E	Adverse Drug Reactions/Events
AMR	Antimicrobial Resistance
CEU	Continuing Education Unit
DTC	Drug and Therapeutics Committee
DI	Drug Information
DIC	Drug Information Center
DIS	Drug Information Service
DTP	Drug Therapy Problem
FMHACA	Food, Medicine and Healthcare Administration and Control Authority
EHSTIG	Ethiopian Hospital Service Transformation Guidelines
ESA	Ethiopian Standards Agency
FMOH	Federal Ministry of Health
GDP	Good Dispensing Practice
HSTP	Health Sector Transformation Plan
SOP	Standard Operating Procedures
TOT	Training of Trainers

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Introduction

Access to authoritative and independent information isfundamental for the rational and effective use of drugs. The serviceranges from the provision of information for the rational choice ofmedicines within a class of drugs to supportformulary review to the selection of an appropriate dosage regimenfor an individual patient. Establishing drug information centers (DIC) at health facilities is very important requirement to make suchservice accessible.The guideline on the establishment of DIC was issued by theformer DACA, now FMHACA in 2004. Since then, various institutions have made efforts to initiate the provision of drug information services (DIS) at publichealth facilities.

Furthermore, because of the issuance of theEthiopian Hospital Reform Implementation Guidelines (EHRIG) ofthe FMOH in 2010 and the health facility minimum regulatorystandards of Ethiopian Standards Agency (ESA) and EFMHACA in 2012 whichhave set the establishment of DIC and provision of DIS as a requirement for health facilities.Due to these efforts,several initiatives have taken place to establish DIC at some health facilities so that they provide accurate, current andunbiased information for the promotion of rational medicine therapy.Equipping DIS with neccesary materials (computers, furnitures and current refernce books)and provision of onsite technical assistances are some of thesupports provided to the establishedDICs.

Pharmacists, require drug information skills to provide evidence-based patient-centered care. Equipping pharmacists with those skills begins in undergraduate programs. Pharmacists may continue to expand drug information skill development throughout their careers through continuing professional development and on-the-job training. Hence, pharmacists practicing DISrequire in-depth knowledge and skill to ensure quality of current, evidence based and objective drug information services they provide. The health facility sssessment on functionality status of DIS at the public hospitals in Ethiopia conducted in August 2017, revealed that although health facilities are providing DIS and pharmacists assigned to provide drug information service, their knoweldedge, skill and attitude in managing queries, searching and evaluating resources, developing and dessiminating information sources, organizing medicine use education sessions and recording, documenting and reporting of DIS activities etc. are limited. In addition, they donot provide poison information and support to pharmacy service activities as they are expected to do so. Furthermore, pharmicists providing DIS didn't take any of on-the-job training on DIS.

Hence, to address these gaps it was foundnecessary and timely to provide in-service training on DIS. Since there is no standardized training manual for the service, it is also crucial to develop in-service training material for DIS so that their capacity in responding to drug information queries, searching and evaluating information resources, organizing educational events, providing poison information, medicines safety etc will be enhanced.By following the principles of instructional design, group of experts in the area designed and developed the drafttraining material considering DI pharmacist's scope of practice, drug informatics course of the undergraduate pharmacy curriculum, authoritative textbooks in the area, previous training materials, other country's training materials and new updates in the field of drug information services.

The course was designed to enhance pharmacy professionals' knowledge, skills, and attitude in critical areas of competencies so that they can meaningfully contribute to provide drug information service. The training material was further enriched by relevant experts from FMOH, universities, hospitals, and development partners.

This national training material contains Participant's Manual, Facilitator's Guide and PowerPoint Presentations.A fundamental shift of training methodology is adopted in this training course. The training course considers participants as the focus of the learning process and as such activities in the sessions are designed to be more trainee-focused. Hence, by and large, a modular approach is followed in the material design, development and it will be implemented in the delivery. Moreover, to give the trainees better practical exposure, hospital DIS visit is included.

Core competency

At the end of this course, participants will acquire the following core competencies: -

Required Knowledge:Overview of Drug Information Service, Sources of Drug Information, Systematic Searching Techniques, Evaluating Drug Information Sources, Managing Drug Information Queries, Step-wise approach in responding to drug information (DI) queries, Production and Dissemination of Medicine-Related Information, Medicine Use Education and Continuing Pharmacy Education, Effective Communication with Healthcare Providers and patients, Source of Poison Information, Role of Drug Information Service in Pharmacy Service Activities, Ethical and legal issues of Drug Information Service, and Quality assurance of DIS.

Required Skill: Effective communication skill, ADE reporting skills, Drug information materials development skill, Documentation and reporting skill, Drug information searching skill, Production and designing of job aids skill, Event organizing skill, and Problem-solving skills.

Required Attitude: Maintain privacy of clients and confidentiality of records, Respect the rights of health care providers and patients, Enhance team spirit and participate in team work, Recognize the importance of advocacy, motivation and dedication, Commitment to provide medicine use education, Believing on the importance of reporting, Willingness to continually develop professionally and get updated with current drug information, Appreciate the contribution for quality of care and patient benefit.

Course Syllabus

Course Description

This 5-days DIS training course is designed for Pharmacists to prepare them provide accurate, up-to-date, timely, unbiased, well referenced, and critically evaluated DIS for healthcare providers, patients/caregivers, and the public.

Course Goal

The goal of this DIS training course is to provide the necessary knowledge, skill, and attitude to pharmacists to address medicine information needs of their clients by effectively searching, evaluating, analyzing, and synthesizing the literature, and appropriately communicating objective drug information to healthcare providers, patients/caregivers, andthe public.

Learning objectives

At the end of this course participants will be able to:

- Identify requirements to establish and/or revitalize DIS.
- Manage medicine information queries properly.
- Produce and disseminatemedicine related information.
- Provide medicine use education to clients.
- Organize continuing pharmaceutical education for health care providers.
- Provide poison information.
- Actively support in pharmacy service activities.
- Follow ethical and legal principles in providing DIS
- Record, report, document and assure the quality of DIS activity.

Learning Methods & Activities

- Interactive lecture
- Reflection
- Small group discussion/exercise
- Role play
- Case study
- Question and answer
- Demonstration
- Individual reading

- Brainstorming
- Site visits
- Teach back session (for TOT)

Learning Materials and Resources

- Participant manual
- Facilitator guide
- PowerPoint presentations
- Learning guides and checklists
- Standard Operating Procedures (SOP)
- LCD Projector
- White board and markers
- Computer(Laptop/Desktop)
- Preprinted case studies
- DIS activity forms
- Flipchart and Markers

Participant Selection Criteria

The target group for this course is pharmacists and clinical pharmacists who will be involved in the provision of DIS, clinical pharmacy service and those who are teaching drug informatics courses.

Facilitator / Trainer Selection Criteria

Facilitators of the first round shall be selected from the national DIS TWG. Trainers for this course should be pharmacists or clinical pharmacists who have DIS TOT training certificate and experiences on drug information service/teaching and clinical pharmacy service/teaching.Trainers of DIS TOT must have experience in adult learning techniques(ALT). Four trainers each staying for the whole duration of the training and one on-job trainer to train the practical session for one day are needed for each training session.

Methods of Evaluation

A. Course Evaluation

- Daily evaluation
- End of training evaluation
- Participant oral feedback

- Post-training debriefing (PTD)
- Post-tests

B. Trainees Evaluation

- ***Formative***
  - Direct observation with feedback
  - Group activities and presentations
  - Individual reflections for questions
  - Case studies
- ***Summative***
  - Progressive assessment (trainee daily performance): -10%
  - Review of trainee's work (a total of 6 assignments) -30%
  - Written exam (post-test) - 60%

Certification Criteria

Certificates will be provided to basic training trainees who have scored 70% and above on summative assessment and attended 100% of the course. For TOT trainees, certificate shall be provided to those who have scored 80% and above on summative assessment and attended 100% of the course.

Course Duration

Five days.

Suggested Class size

Suggested training class size: shall not be more than 20 - 25 participants per training venue

Training Venue

The training will be conducted at the nationally recognized IST centers with adequate computer and uninterrupted internet access. As much as possible, the computer to trainee ratio shall be one-to-one. The venue shall be selected considering the availability of good facility for the site visit or transportation service shall be arranged for the visit ahead of time.

Course Schedule

Training Course on Drug Information Services for Pharmacists

Organized by:_____

Venue: _____ **Date:** _____

Time	Topic	Presenter/Facilitator	min
Day One: _____			
8:30-9:00	Registration of participants	Organizers	
9:00-10:00	Welcoming Address/Opening Speech/Gallery of Experts		90
10:00-10:30	Pretest		
10:30-10:45	**Tea Break**	**Organizers**	15
10:45-11:25	**Overview of Drug Information Services:** Global and National Experiences		40
11:30-12:05	**Overview of Drug Information Services:** Functions and requirements to establish DIS		35
12:05-12:30	Discussion	Participants/organizers	15
12:30-2:00	**Lunch Break**	**Private**	
2:00-3:10	**Sources of Drug Information:** introduction, Tertiary sources of DI		70
3:10-3:30	**Sources of Drug Information:** SecondarySources of DI		20
3:30-3:45	**Tea Break**	**Organizers**	
3:45-4:45	**Sources of Drug Information:**Secondary Sources of DI		60
4:45-5:15	**Sources of Drug Information:**PrimarySources of DI		30
5:15-	Daily evaluation and administrative messages	Participants/organizers	
Day Two: _____			
8:30-9:00	Recap of Day One	Participants/organizers	
9:00-9:45	**Sources of Drug Information:**PrimarySources of DI		45
9:45-10:30	**Sources of Drug Information:** Alternative Sources of DI		45
10:30-10:45	**Tea Break**	**Organizers**	
10:45-11:15	**Sources of Drug Information:** Alternative Sources of DI		30
11:15:11:45	**Sources of Drug Information**: Guidelines as a source of DI and summary		30
11:45-12:00	Discussion on Sources of information	Participants/organizers	15
12:00-12:30	**Managing Drug Information Queries:** introduction and Step-wise approach to answer		30

Time	Topic	Presenter/Facilitator	min
	queries		
12:30-2:00	**Lunch Break**	**Private**	
2:00-3:10	**Managing Drug Information Queries:** Step-wise approach to answer queries		70
3:10-3:30	**Managing Drug Information Queries:** Formulating response and recommendations		20
3:30-3:45	**Tea Break**	**Organizers**	
3:45-4:40	**Managing Drug Information Queries:** Formulating response and recommendations and summary		60
4:40-5:25	**Production and Dissemination of Medicine-Related Information:**introduction and steps of Professional writing		45
5:25-	Daily evaluation and administrative messages	Participants/organizers	
Day Three: _____			
8:30- 9:00	Recap of Day Two	Participants/organizers	
9:00-10:30	**Production and Dissemination of Medicine-Related Information:** preparation and dissemination of information		90
10:30-10:45	**Tea Break**	**Organizers**	
10:45-11:30	**Production and Dissemination of Medicine-Related Information:** preparation and dissemination of information		45
11:30- 11:45	**Production and Dissemination of Medicine-Related Information:**Dissemination of informationand summary		15
11:45-12:30	**Medicine use Education and Continuing Pharmacy Education:** Introduction and medicine use education(basic principles & phases)		45
12:30:2:00	Lunch		
2:00-2:30	**Medicine use Education and Continuing Pharmacy Education:** Introduction and medicine use education(basic principles & phases)		30
2:30-3:30	**Medicine use Education and Continuing Pharmacy Education:** Introduction and organizing CPE events, Effective communication with health care providers and patients		60
3:30-3:45	**Tea Break**	**Organizers**	
3:45:4:30	**Poison Information Service:** Introduction, Global and National Magnitude of poisoning		45
4:30-5:15	**Poison Information Service:**Sources of poision information and Poison Management Information Service		45
5: 15-	Daily evaluation and administrative messages	Participants/organizers	
Day Four: _____			
8:30- 9:00	Recap of Day Three	Participants/organizers	

Time	Topic	Presenter/Facilitator	min
9:00-9:30	**Poison Information Service:**Sources of poision information and Poison Management Information Service cont.		30
9:30-10:30	**Poison Information Service:**Job aid for common poision Management and summary		60
10:30-10:45	**Tea Break**	**Organizers**	
10:45-11:45	**Role of DIS in Pharmacy Service Activities:** Introduction and Pharmacovigilance		60
11:45:12:30	**Role of DIS in Pharmacy Service Activities:** DTC, Formulary, DUE and AMR		45
12:30-2:00	**Lunch Break**	**Private**	
2:00- 2:40	**Role of DIS in Pharmacy Service Activities:** CP, DSM and Summary		20
2:40-3:30	**Ethical and legal issues of DIS:**Introduction and Basic legal and ethical principles		50
3:30-3:45	**Tea Break**	**Organizers**	
3:45-4:05	**Ethical and legal issues of DIS:**Basic legal and ethical principles cont.		20
4:05-5:15	**Ethical and legal issues of DIS:** Specific ethical and legal issues related to DIS, case study and summary	Participants/organizers	70
5:15-	**Orienation on DIS planning,**Daily evaluation and administrative messages	Participants/organizers	
Day Five: _____			
8:30- 9:00	Recap of Day Four	Participants/organizers	
9:00-10:30	**Quality assurance of DIS:** Introduction, components of QA in DIS and documenting and reporting DIS activities		90
10:30-10:45	**Tea Break**	**Organizers**	
10:45-11:30	**Quality assurance of DIS:** Monitoring and evaluation, DIS indicators and summary		45
11:30-12:30	**Getting Started:**Introduction, Stepwise approach to start and revitalizing DIS		60
12:30-2:00	**Lunch Break**	**Private**	
2:00-3:00	**Getting Started:**Promotion and Advocacy of DIS and Planning to establish/revitalize DIS		60
3:00-3:30	Post Test/Course Evaluation	Participants/organizers	30
3:30-3:45	**Tea Break**	**Organizers**	
3:45-	Certification, Group picture and Closing Remarks	Participants/organizers	

Chapter One: Overview of Drug Information Service

Chapter Description: In this chapter the participants will be introduced to the overview of global and national status of drug information service. Furthermore, the participant will describe the functions DIS and identify the requirements to establish drug information service.

Chapter Objective: At the end of this chapter the participants will be able to describe theoverview of drug information service.

Enabling Objectives: At the end of this chapter, participants will be able to:

- Explain global and national status of drug information service.
- Describe the functions of drug information service.
- Identify requirements to establish drug information service.

Chapter Outline:

This chapter has the following outlines:

- Global and national status of drug information service.
- Functions of Drug Information Service.
- Requirements to establish Drug Information Service.

Allocated Time90 minutes

Definitions

Drug Information (DI):	Is written and/or verbal information on pharmaceuticals and therapeutic use of medicines.
Drug Information Service (DIS)	Is the provision of anup-to-date, unbiased, well referenced,andcritically evaluated therapeutic, and pharmaceuticalinformation. It also includes provision of education,training, and conductingresearch.
Drug Information Center (DIC):	Is a unit designated for providing drug information service
DI Pharmacist:	Is a pharmacist responsible for operating a DIC and providing DIS.

1.1. Global and national status of drug information service

The provision of medication information is among the most fundamental responsibilities of pharmacists. The information may be either patient specific, as an integral part of pharmaceutical care, or relative to a group of patients, such as in the development of a therapeutic guideline, publishing an electronic newsletter, or updating a website.

The pharmacist is in an ideal position between physician and patient. As such, pharmacists must be knowledgeable and confident while interacting with physicians, other healthcare professionals, public and patients. Thus, the aspect of providing unbiased, evidence based and up-to-date written and oral information for healthcare professionals and others has resulted in an increasing demand for independent drug information pharmacists.

1.1.1. Global Experiences of Drug Information Service

In 1962, the first drug information center was opened at the University of Kentucky Medical Center. The center was expected to take an active role in the education of health professional students including medicine, dentistry, nursing, and pharmacy. A stated goal was to influence pharmacy students in developing their role as drug consultants. Several other drug information centers were established shortly thereafter. In Europe the first DICsestablished in Germany in 1960s then after in the 1970sin the UK and Sweden.The pioneers in providing drug information in India were the Karnataka State Pharmacy Council (KSPC) and the Ooty and Thiruvananthapuram

medical colleges.Following this trend, many DICs were initiated in India. In developing countries, DIS is still a new concept.

1.1.2. National Experiences of Drug Information Service

Considering the global move and, there was a need to provide unbiased, up-to-date, timely and accurate drug information services to the health care professionals, patients and the public, Food, Medicine and Healthcare Administration and Control Authority (FMHACA), former Drug Administration and Control Authority of Ethiopia (DACA), has been providing regulatory drug information bulletin, posters, brochures, and radio and also issued the guideline on the provision of drug information service in 2004. Since then efforts have been made by various institutions to initiate the provision of DIS at public health facilities.

Furthermore, in line with the national pharmacy curriculum revision process, the School of Pharmacy/Addis Ababa University (SOP/AAU) established a model DIC at Tikur Anbessa Specialized Hospital in 2009 and provided DISin partnership with Howard University College of pharmacy through twinning center, with the aim of serving as a center of excellence on drug information services in Addis Ababa. Since then efforts have been made by various institutions to initiate the provision of DIS at public health facilities including St. Paul's Hospital Millennium Medical College which was officially started provision of DIS in March 2010.

Furthermore, the following guidelines and standards have set the provision of DIS as a requirement for health facilities:

- The Ethiopian Hospital Reform Implementation Guidelines (EHRIG) in 2010 and its revised version, Ethiopian Hospital Services Transformation Guidelines (EHSTG) in 2017,
- Ethiopian Health Center Reform Implementation Guideline (EHCRIG) in 2014,
- The health facility minimum regulatory standards of Ethiopian Standards Agency in 2012

The initiation of clinical pharmacy service and issuance of national DIS SOP are also important milestones towards the provision of DIS.Following theseinitiatives, hospitals and teaching institutions have started providing DIS. Several other drug information services established shortly thereafter leading more than 126 DIS in Ethiopia by a concerted effort of PFSA in collaboration with USAID/SIAPS. In addition, private institutions have also initiated provision of DIS. These include Tossa Pharmacy DIC at Dessie and Gishen Pharmacy DIC in Addis Ababa.

Activity 1.1 Brainstorming on DIS	
	Did your facility establish DIS? If Yes, what are the challenges you face while establishing and running DIS? If No, what are the reasons?

Despite these efforts there are some challenges in establishing and running DIS. These include lack of adequate space to run the DIS and internet access directly to the DIS Unit, shortage of latest version reference books, poor management, and DTC support for the DIS, poor commitment from the service provider and lack ofadditional materials to run the DIS such as photocopy machine, color printer, and projector.

1.2. Functions of Drug Information Service

Acttivity 1.2 Probing question on Functions of DIS	
	What are the functions of DIS?

DI pharmacistsshould understand the scope and functions of drug information services to provide the servicesproperly. The DIS are involved in the provision of therapeutic and pharmaceutical information, education and training, dissemination of medicine information, research, support pharmacovigilance program, provision of poison information, and supportother pharmacy service activities.

1.2.1. Therapeutic and Pharmaceutical Information

The primary function of a DIS is provision of an efficient clinical enquiry answering and advice on all aspects of medicines use and therapeutic information. Hence, itoffers patient-related drug information on efficacy, optimum dosage, interactions, adverse effects, mode of administration, effects of other diseases, poisons management and strategies to promote adherence to treatment schedules. Most other enquiries will relate to pharmaceutical preparations generally and include issues of availability, formulation, cost, storage and stability. The DIS should support the provision of clinical pharmacy service in the facility through providing the necessary medication information.

1.2.2. Education and Training

Educational activities are important to support the rational use of drugs. Providing medicine information to health professionals and patients/the public is part of the functions ofDIS. A drug information service can facilitate and provide continuing education sessions to health care professionalsand targeted medicine use education to the public andserve as practical sites for undergraduate and graduate health science students.

1.2.3. Dissemination of Information

DIC/DIS should be involved in preparation and dissemination of written drug information in the form of brochures, fliers, posters, bulletins, leaflets, newsletters, drug inclusions/exclusions, drug alerts and electronic media through the internet, radio, television, etc. to health care providers and patients/community.

1.2.4. Operational Research

Drug information services should be involved in operational research activities including medication utilization studies.

1.2.5. Pharmacovigilance

Quick identification and communication of potential problems to healthcare team may improve patient safety. DIS often have a role in programs, which prevent, detect, recognize, manage, document and report ADEs -due to medication errors, ADRs and product defects.

1.2.6. Poison Information

Drug information services provide information and advice on the diagnosis and treatment of poisonings. Suitable information on the management of any poison situation, including household products, poisoning plants and animals, medications and other chemicals should be available to health professionals and the public.

1.2.7. Involvement in Pharmacy Service Activities

Drug information pharmacists are also expected to involve in pharmacy service activities (DTC, clinical pharmacy and drug supply management etc.) in the preparation and revision of facility-specific medicines list, preparation of educational materials on rational medicine use, provision of education on medicine use, providing updated information to clinical pharmacists, stock status analysis, and undertaking drug use studies.

1.3. Requirements to Establish DIS

Activity 1.3 Plenary discussion on requirements to establish DIS	
	What are the requirements to establish DIS?

To ensure optimal operational performance and quality provision of drug information service, appropriate personnel, adequate space, equipment and supplies should be available for all professional and administrative functions relating to DIS. These resources must be located in areas that facilitate the provision of services to healthcare providers and patients/community. According to National Standard Operating Procedures (SOP) manual for the provision of DIS and guideline for establishment and operation of a DIC, the following are some of the requirements needed to establish and run DIS.

1.3.1. Personnel

The number of personnel required will depend on the range of activities offered and the hours of service. The health facility should assign at least one full-time pharmacist. The drug information pharmacist(s) should have competent knowledge in clinical use of medicines. Furthermore, they shall acquire basic skills in communication, data storage and retrieval, literature evaluation, bulletin writing, computer usage, information sourcing, clinical interventions, and documentation and report writing.

1.3.2. Facilities and Equipment

Basic facilities required for a DIS include:

- Dedicated and accessible room;
- Furniture – desks, chairs, shelves;
- Communications – telephone, internet access;
- Computer, printer and accessories
- SOPs Manual and DI formats

Availability of other supplies such as photocopier, color printer and fax machine facilitate the DIS activities. A dedicated area must be set aside for the DIS that is accessible to the users. Allocated space should be sufficient for reference collection, storage and provision of the service.

1.3.3. Reference Materials

The DIS should maintain basic up-to-date drug information reference materials (hard copy and/or electronic copy). These include textbooks and up-to-date international and national guidelines, databases, reports and scientific journals. Information from previous enquiries can also be used.

1.3.4. Finance

The health facility should allocate adequatebudget for proper functioning of the DIS. Capital equipment and management costs should be included in the budget. Sufficient expenditure to maintain up-to-date resources is essential for the long-term viability of the center.

Chapter Summary:

- The provision of medication information is among the most fundamental responsibilities of pharmacists.
- The first drug information center was opened at the University of Kentucky Medical Center in 1962.
- The first DIC in Ethiopia was established to provideDISat Tikur Anbessacomprehensive specialized hospital in 2009.
- DIC should be involved in the provision of therapeutic and pharmaceutical information, education and training, dissemination of medicine information, research, provision of poison information, and support pharmacy service activities.
- To establish the service and ensure optimal operation;dedicated DI pharmacist, dedicated adequate space/room, and adequate information resources, equipment and supplies should be available.

Chapter Two: Sources of Drug Information

Chapter Description: This chapter enables the participants to understand the three common sources of drug information (tertiary, secondary and primary). Within each source of drug information, the common examples, advantages and disadvantages, how to systematically search and how to evaluate drug information and their sources will be discussed in detail. Finally, alternative sources of drug information such as the internet and other sources of information will be dealt.

Chapter Objective: By the end of this chapter, participants will be able to identify, systematically search and evaluate tertiary, secondary, primary, and alternative drug information sources.

Enabling Objectives: By the end of this chapter, participants will be able to:

- Differentiate between primary, secondary, and tertiary sources of information.
- Determine appropriate sources for a specific information request.
- Search the required sources of drug information.
- Evaluate resources to determine appropriateness of information.
- Recognize alternative sources for provision of drug information.

Chapter Outline:

This chapter has the following outlines:

- Tertiary sources of drug information
- Secondary sources of drug information
- Primary sources of drug information
- Alternative sources of drug information

Allocated Time: 330 minutes

2.1 Introduction

The quantity of medical information and medical literature available is growing and the technology by which this information can be accessed is also improving exponentially. The introduction of tablets, smartphones, and internet resources has radically changed the methods and technology by which information is accessed, but not the process of providing drug information.

There are three types of drug information resources, namely tertiary, secondary, and primary. In general, the best method to find information includes a stepwise approach moving first through tertiary, then secondary, and finally primary literature (general-to-specific approach). If the information obtained in the tertiary resources is not recent or comprehensive enough, a secondary database may be used to direct the reader to review primary literature articles that might provide more insight into the topic. For some requests, it may be necessary to consult internet sites or news reports to get background information before beginning the formal searching process. Also, other resources, including experts' areas of practice may need to be consulted.

However, often a search for information does not employ these steps and does not require the use of all three types of resources. For example, a question regarding local availability of a product formulation, or mechanism of action of a drug, could quickly be found in a local retail/import/ manufacturer and tertiary resource. The information found there may be sufficient to conclude the search and provide response. However, a question regarding the clinical trials supporting off-label use in a specific population will likely require a search of primary literature.

Pharmacists are being asked daily to provide responses to numerous drug information requests for a variety of people. It is tempting just to select the easiest, most familiar resources to find information;however, in doing so, there is a possibility of missing new resources or limiting the comprehensiveness of the information found. For these reasons, identification of appropriate sources of information with systematic approach of searching and evaluation of the sources obtained are crucial. It is for these reasons that evaluation of information sources is important to streamline the search process.

2.2 Tertiary Sources of Drug Information

2.2.1 Introduction

Tertiary sources provide information that the author or editor has summarized and distilled to provide a quick easy summary of a topic. These references may often serve as an initial place to identify information, because they provide fairly a complete and concise overview of information available on a specific topic. Examples include:

- Textbooks, compendia, review articles in journals, and other general information found on the internet.

- Computerized tertiary sources include Micromedex®, up-to-date® and Lexi-comp®.

Figure 2.1 Examples of common tertiary sources

For additional references, see annex 2.1.

- **Advantages**
  - Convenient, easy to use, and familiar to most practitioners.
  - Most of the information needed by a practitioner can be found in these sources, making it excellent first-line sources of information when dealing with a drug information question.

- **Limitations**
  - Lag time associated with publication, resulting in less current information. Medical information changes so rapidly that the information may be out of date before it is even published. However, electronically available tertiary resources have helped this situation.
  - Information in a tertiary text may be incomplete, due to either space limitations of the resource or incomplete literature searches by the author.
  - Errors in transcription, human bias, incorrect interpretation of information, or a lack of expertise by authors.

For these reasons, readers must judge the quality of tertiary references and may need to verify the information in multiple sources (see evaluating DI sources).

2.2.2 Systematic Searching of Tertiary Sources

As said earlier, tertiary sources are usually an entry point while looking for a drug information. Within the tertiary sources, you start with core general references (major compendia), such as Drug Facts and Comparison, Physician Drug Reference (PDR), AHFS Drug Information, Micromedex, Lexicomp®, Clinical Pharmacology and Textbooks before you search for specific references. The specific tertiary references include:

- ‘Meyler’s side effects of drugs’ will be used for queries related to side effects.
- ‘Hansten and Horn’s drug interaction’ is a classic gold standard resource on drug interactions, analysis and management, and
- ‘Brrig’s: Drugs in Pregnancy and Lactation is used as source of information on the safety of drugs during pregnancy and lactation.
- ‘Pharmacotherapy (Dipiro)’ is a source of information on disease management (therapeutics),
- ‘Goodman & Gilman’s’ is a source of information on pharmacology and pharmacological approach of therapeutics,

Furthermore, selecting a resource focused on the type of information needed for a specific request or situation is also important. For example, a very well-written and comprehensive therapeutics text may have very limited use in providing information regarding pharmacokinetics of a specific drug. For this reason, it is important to consider the *categories of requests.*

The type of requestor may also influence the resources used to respond the question. Generally, a request from a consumer or patient could more appropriately be answered from available tertiary

resources than from a stack of clinical trials. However, if the requestor is a prescriber requesting detailed information about the management of uncommon specific disease state and role of investigational therapies, searching and use of primary literature may be appropriate.

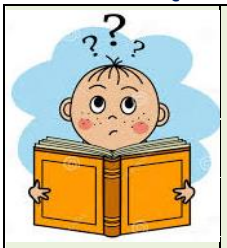
While looking for them, tertiary sources could be available either in a paper text or via a variety of electronic formats.The electronic resources could be available online or offline. Electronic resources are often preferred because they may be easier to use, allow quicker access to information, allow multiple searches to be performed simultaneously, and often contain the most recent information. Additionally, many electronic networked resources allow use of the same resource at more than one location, which allows pharmacists access information from a variety of locations.

Finally, if the information obtained in the tertiary resources is not recent or comprehensive enough, a secondary database may be used to direct the reader to review primary literature articles that might provide more details into the topic.

2.2.3 Evaluating Tertiary Literature

Since tertiary reference source have limitations which have been mentioned above, readers must judge the quality of tertiary references. Some questions that should be considered when evaluating tertiary literature are listed below.

Table 2. 1 Questions that should be considered when evaluating tertiary literature

	• Does the author have appropriate experience/expertise to publish in this area? • Is the information likely to be timely based on publication date? • Is information supported by appropriate citations? • Does the resource contain relevant information? • Does the resource appear free from bias and blatant errors?

Case Study 2.1 -Determining appropriate tertiary sources	
	A 15-year-old patient has recently been started on atomoxetine for treatment of attention deficit/hyperactivity disorder (ADHD). He is taking no other medications. He has noted recently that his hair is thinning and wants to know if this might be drug related.
• *What are appropriate tertiary resources to consult for a response to this request?* • Try to find the answer on the resource you selected for the above question.	

Case Study 2.2 -Determining appropriate tertiary sources	
	A new mother has been breast-feeding her child for 3 months. The mother has recently been prescribed levofloxacin for treatment of an infection.
• *What sources should be consulted to determine the appropriateness of this choice?* • Try to find the answer on the resource you selected for the above question.	

2.3 Secondary Sources of Drug Information

2.3.1 Introduction

Secondary sources of information refer to resources that provide indexingand/or abstracting servicesof the primary literature, with the goal of directing the user to relevant primary literature. There are two commonly used terms when we talk about secondary information resources, indexing and abstracting. The two terms differ slightly; Indexing consists of providing bibliographic citation information (e.g., title, author, and citation) of the primary article, while abstracting, includes a brief description (abstract) of the information provided by the article or resource cited. Examplesof secondary resources include:

- **MEDLINE/PUBMED**; which is maintained by the National Library of Medicine (NLM) of the National Institute of Health (NIH) of the US. NLM is the world's largest medical library and it is the creator of MEDLINE.
- **The Cochrane Library;** it is named in honor of Archie Cochrane; a British researcher and the library is found by the Cochrane Collaboration which is an international network of more than

28,000 individuals from over 100 countries. It is a database of systematic reviews and contains thousands of reviews and articles.

- **Google scholar;**provides a simple way to broadly search for scholarly literature. From one place, you can search across many disciplines and sources: articles, theses, books, abstracts and court opinions, from academic publishers, professional societies, online repositories, universities and other web sites.

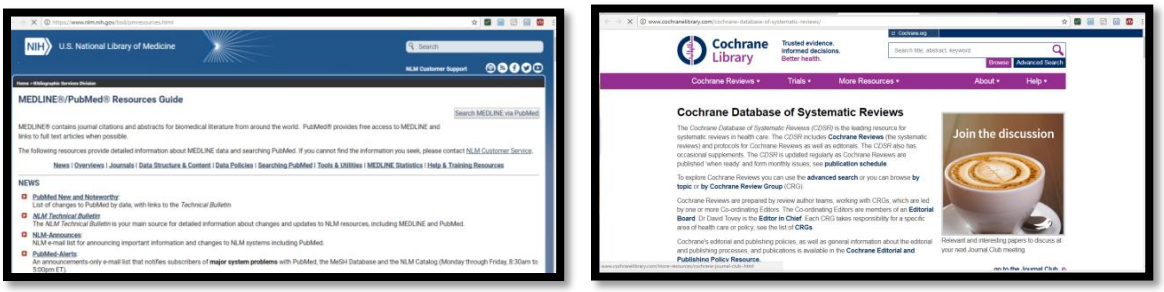


Figure 2.2 Webpages for some of secondary sources

The exhausted list of secondary resources is annexed in Annex 2.1.

- **Advantages**
  - It provides indexing and abstracting services
  - The information available in abstracts may be entirely appropriate and wholly adequate to draw conclusions and answer the question in short period of time.
  - It is easily searchable
  - Mostly it is computerized (majority of them are utilized primarily in an electronic format, although some may still have a print form).
  - It is user-friendly
  - It covers thousands of articles (for instance in PUBMED)

- **Limitations**

While searching secondary databases, systems do not index all terms the same. So, it is necessary/important to determine what terms a database is using to conduct a successful search.

  - For example, databases through the NLM index terms by their Medical Subject Heading (MeSH), called MeSH terms.

- However, most computerized databases also include a free-text search option, which is very useful when the defined index terms are not known or do not identify relevant data. This option may also be helpful when the term is newly emerging or before an official index term is defined. Hence, it is important to utilize a variety of terms for search strategy.

2.3.2 Systematic Searching of Secondary Sources

In searching most databases, a relatively similar search strategy can be followed. Electronic searches generally use the **Boolean operators**: AND, OR, and NOT (Figure 2.3).

- The operator **AND** will combine two terms, returning only citations containing both of those concepts or terms.
- Combining two terms with the operator **OR** will result in an equal or greater number of returns since it will include any citation where either term is used.
- The term **NOT** should be used with caution as it always decreases the number of returns. It eliminates any references having that term and may eliminate appropriate articles simply because the term happens to appear somewhere in the article.

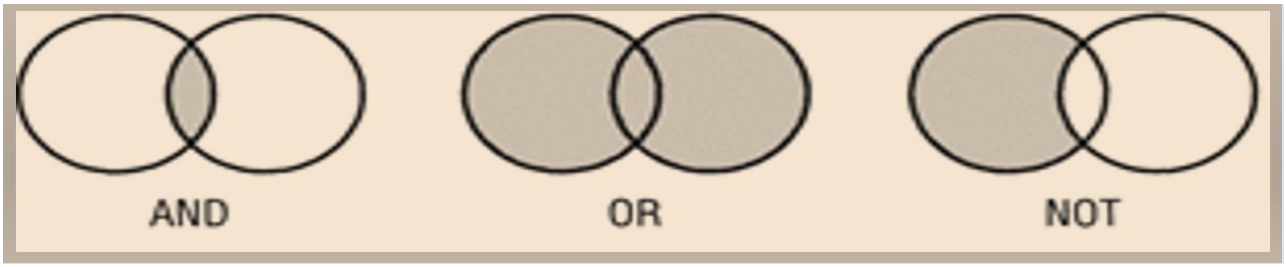


Figure 2.3. Boolean operators

The following table illustrates the operation of Boolean terms

Table 2.2. Example how to use Boolean operators

AND	OR	NOT
Each result contains **all** search terms.	Each result contains **at least one** search term.	Results **do not contain** the specified terms.
The search h*eart***and** lungfind items thatcontain **both***heart*and *lung*.	Thesearch *heart***or** *lung* finds items that contain **either***heart***or** items that contain *lung*.	Each *heart* **not** *lung* finds items that contain *heart***but do not contain** *lung*.

2.3.3 Evaluating Secondary Sources

Globally, there are a lot of secondary databases which provide drug information. Hence, it might be wise enough to select some of them and become familiar with their content and searching techniques. In doing, so it is very important to first evaluate the database itselfand hence the contents there in. while evaluating the contents of the databases, the information in the specific work should meet the required academic standard.It is important to detect biases, and an introduction or preface will usually give an idea of the point of view of the writer. There are also ways to determine if a secondary source is accurate and credible; use other secondary sources to verify the information and to check the list of references used by the author. The reference list can tell you the type of sources used and how they can be verified. Finally, the publisher shall be checked that only works of high quality are published.

Case Study 2.3 Determining information resource for Boolean operators	
	A physician requests information about the use of Sildenafilfor treatment of female sexual arousal disorder. She also requests information about use of any of the other phosphodiesterase-5 inhibitors.
▪ *What resources might be good to look for this information?*	

Case Study 2.4 Identifiying key terms for Boolean operators	
	A physician asked if Metoclopramide could increase milk production. He also requested to compare the effect of Domperidone with Metoclopramide on breast milk production (output)
○ *Which Boolean operators will you use to respond for the above requests?* ○ *How could you search results that exclude "formula milk"?* *Instruction:* 1. Identify key search terms. 2. Search the information without using Boolean operators and see the result. 3. Search using Boolean operators to connect key terms and see the result. 4. Compare the number of results in both searching techniques.	

2.4 Primary Sources of Drug Information

2.4.1 Introduction

Primary sources also called primary literature often provides the most recent and in-depth information about a topic and allows the reader to analyze the study methodology to determine if the conclusions are valid. A primary source is one in which the authors directly participated in the

research or documented their personal experiences. Many, but not all, papers published in journals are primary sources for facts about the research and discoveries made. Examples of primary literatures include:

- Clinical original research studies and reports, both published and unpublished.
- Publications including controlled trials, cohort studies, case series, and case reports.

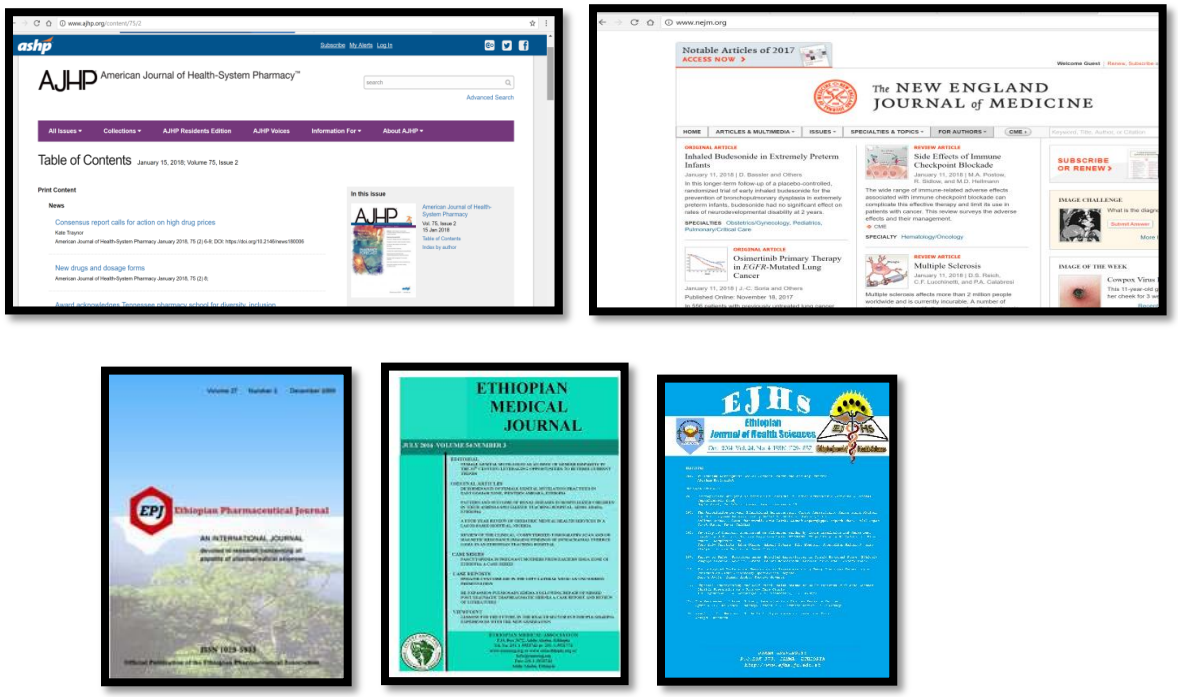


Figure 2.4Primary sources of information

Common international and local journals that contain primary literatures are listed below.

Table 2.3. Common primary sources

- American Journal of Health-system Pharmacists (AJHP)- http://www.ajhp.org/
- Annals of Pharmacotherapy: https://www.ncbi.nlm.nih.gov/labs/journals/ann-pharmacother/
- Hospital Pharmacy Formulary: https://www.ncbi.nlm.nih.gov/labs/journals/hosp-formul/
- New England Journal of Medicine (NEJM)- http://www.nejm.org/
- Journal of the American Medical Association (JAMA)- https://jamanetwork.com/
- British Medical Journal- http://www.bmj.com/
- Annals of Internal Medicine –http://www.annals.org/aim
- Ethiopian Pharmaceutical Journal: https://www.ajol.info/index.php/epj
- Ethiopian Journal of Health Development: www.ejhd.org/
- Ethiopian Medical Journal - http://www.emaethiopia.org/, www.emaemj.org/

- Ethiopian Journal of Health Sciences- https://www.ejhs.ju.edu.et/

- **Advantages**
  - Access to detailed information about a topic and the ability to personally assess the validity and applicability of study results.
  - Primaryliterature tends to be more recent than tertiary or secondary literature.

- **Disadvantages**
  - Misleading conclusions might be reached if only one study is used without the context of other researches, the need to have good skills in medical literature evaluation, and the time needed to evaluate the large volume of literature available.
  - It is also difficult to determine which journals are essential in a pharmacy practice setting due to the rapidly increasing number of specialty journals being published.

2.4.2 Systematic Searching of Primary Sources

Once the required literature has been identified in a secondary searching system, the actual articles can be obtained in various ways. These include:

1. Many databases like PUBMED link users directly to the article of interest through PUBMED central (PMC).
2. Free articles can be accessed through HINARI for developing countries.
3. Some publishing journals may also provide directly for free before going to PMC or HINARI.
4. Google scholar can also provide you some articles for free.

For example, PUBMED links users to open access journal publications and articles through PubMed Central (http://www.pubmedcentral.nih.gov/). The following is a stepwise approach to search articles using PUBMED central.

Step1: Go to the Google browser and write the link for "PubMed central"

(http://www.pubmedcentral.nih.gov)

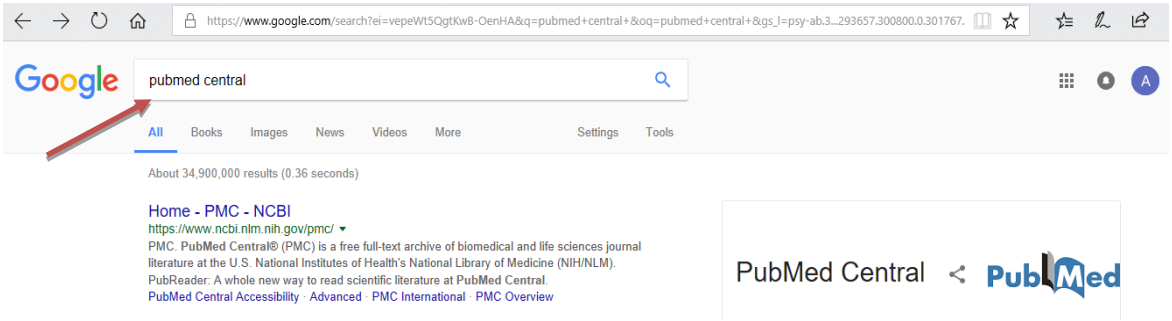


Figure 2.5. Browsing Pub med central step 1

Step 2: Click on the home page for PubMed central (http://ncbi.nlm.nih.gov/pmc).

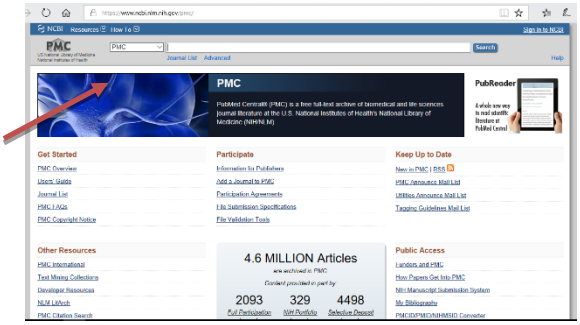


Figure 2.6. Browsing PubMed central step 2

Step 3:Search the article title you got from other secondary sources like PUBMED or write key terms of your interest, for in instance "Azithromycin in the management of community acquired pneumonia in pediatrics" on the search bar. Several articles related with the search will be listed in the search result. Then see if the article of your interest is free in PMC. If so download and enjoy reading.

NB: All of these solutions of finding a primary article are not 'complete solutions' by their own. They just provide partial solutions. So, try your best in all possible ways to find a free article. But, don't forget that articles published on some journals including open access journals are available freely without such complex process, even in a single hit on google.

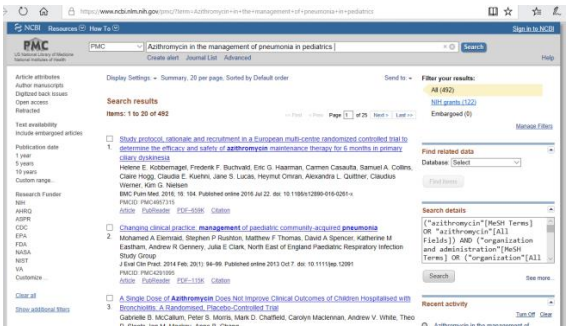


Figure 2.7. Browsing PubMed central step 3

2.4.3 Evaluating Primary Literature

There is a wide range of journals available that can assist the pharmacist in keeping up todate in the different aspects of pharmaceutical practice. Although medical journalsare peer-reviewed, do not assume that because a review article or researched studyappears in print it is necessarily good science.

Generally, the following points can be used to determine if an article published is authoritative:

- What is the author's qualification for writing on the subject?
- Is the author connected to an organization with an established reputation?
- Look for the source. Is it a major university or institute specializing in that area?
- Is it published on a reputable website? Has it been peer-reviewed?
- Has the author taken care in formatting, logic, structure, and development of the argument?

As a general guide, evaluation of each information sources and study types follow own checklist. Examples of specific evaluation checklists i.e. Questions for evaluation of information sources, Checklist to appraise systematic literature review and Questions for evaluating Clinical Trialsare attached in Annexes 2.2, 2.3 and 2.4 respectively.

Activity 2.1Exercise on critical appraisal of meta-analysis (systematic review)

Consider the systematic review by D. Wilkinson et al. entitled "Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomized placebo-controlled trials" (see Annex2.5).

Instruction: Use the clinical trials checklist provided in Annex 2.3 to appraise the review.

Activity 2.2 Exercise on Critical Literature Appraisal:

Pfeffer. M.A. et al, Effects of Candesatran on Mortality and Morbidity in patients with chronic heart failure: the CHARM Overall program. Lancet 2003. 362: 759-66. (See Annex 2.6)

Instruction: Perform Critical literature evaluation using the checklist Annexed on Annex 2.4

2.5 Alternative Sources of Drug Information

2.5.1 Internet Sources

Introduction

At times, even well-designed searches of standard medical literature do not yield sufficient information to make clinical decisions or recommendations. In these cases, alternative resources may need to be employed. One such method to identify relevant source or information might be a general internet search.Examples:

- The most commonly used internet search is using a search engine google (http://google.com). In addition, Yahoo (http://yahoo.com) search engine can be used.
- For searching scholarly articles, google scholar can be used (http://scholar.google.com).

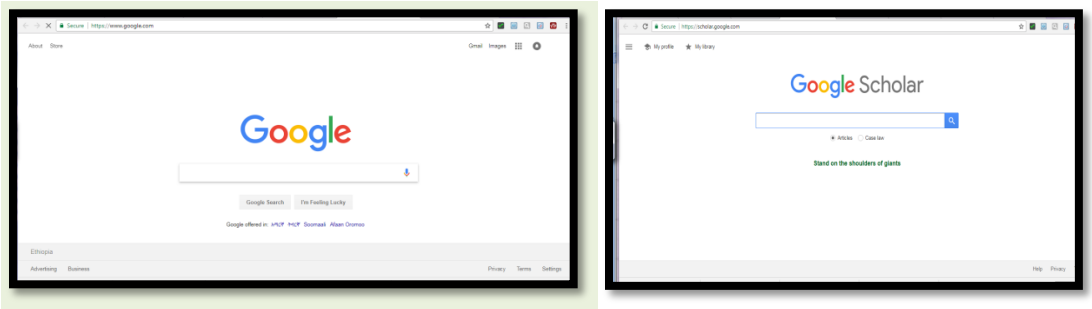


Figure 2.8 Common internet searching engines

- **Advantages**
  - Serve as a starting point for questions about uncommon diseases, new terms, drugs in development, or marketed OTC products and combination dietary supplements.
  - It is useful for topics that have recently been in the news, where information is changing more rapidly than standard paper resources.

- **Limitations**
  - As anyone can put any information on the web, information retrieved from the internet must be evaluated and analyzed for appropriateness.
  - It needs skill to evaluate the information on the web.
  - There is no a true evaluation mechanism for the information on the web. Because, to assess quality of online information, several standards and programs exist (it will be discussed later).

Searching the Internet

It is important to remember that different search engines use different techniques to identify Web pages, and that no search engines identify all Web sites. Popular web browsers include;

- Microsoft Internet Explorer (http://www.microsoft.com),
- Firefox (http://www.firefox.com)
- Opera (http://www.opera.com).
- Chrome (http://google.com/chrome)
- Metasearch engines

However, there are some search engines, which are geared toward scholarly content (such as Google Scholar, http://scholar.google.com) or scientific research, rather than general information. These might be more useful for identifying recent research about a disease or disorder.

To efficiently perform a search, it is important to consider which search engine would most likely index the desired materials.

Evaluating information on the web

Finding the information is only part of the battle. Essentially anyone can put any information on the web, whether that information is valuable, worthless, disgusting, or even dangerous. A web source should be evaluated for believability, the source (author), supporting evidence, logic, timeliness, and other factors. There are millions of web sites and there are no true quality assurance measures in place to evaluate the reliability of information available. There are some general views to keep in mind when evaluating this type of literature.

Generally, sites maintained by educational institutions, not-for-profit medical organizations, or a division of government are likely to contain high-quality information, whereas information maintained by a company selling/promoting a specific product may be more questionable.

- **High Quality**: Government *(.gov),* education *(.edu),* professional association *(.org),* military *(.mil);* news services
- **Medium Quality**: Pharmaceutical manufacturers *(.com)*
- **Low Quality**: individuals, selling ideas or products*(.com)*

To assess quality of online information several standards and programs now exist. These include organizations such as the Health on the Net (HON code, http://www.hon.ch), which clearly define

rules to evaluate the quality of information available via a web site. These organizations do not evaluate every web site available, but instead only those who request evaluation.

Health on the Net Foundation has established an **HONcode** (http://www.hon.ch/HONcode/conduct.html), which contains principles**.** These principles, if met, support the quality of the information provided by a website.A webmaster for a site can apply to the Health on the Net Foundation to display their **HONcode logo** on a website. Since many Web sites do not request evaluation, the lack of an organization's quality seal does not necessarily indicate that the information is of low quality.

We comply with the HONcode standard for trustworthy health information - verify here

Figure 2.9. HON code Log

Many health sites explain the criteria used for including material within the website. Essential Health Links gateway reviews each potential link using a list of required criteria. See: http://www.healthnet.org/essential-links/about.html

The following criteria should be used when determining quality of online material:

Table 2. 4 Questions that should be considered when determining quality of online material:

- Is the source credible, without a personal stake in promoting one treatment or product?
- Is the information accurate and current
- Does the site link to other nonaffiliated sites that provide consistently good information
- Is the information appropriately detailed and referenced
- Is it possible to identify the author of the site to contact with additional questions or comments?

2.5.2 Consumer Health Information

As consumers become more active in their health care and more computer literate, the demand for health information sources designed for consumers has been increasing. Currently there are varieties of sources where consumers obtain their health information. Since many consumers find at

least some of their information online, pharmacists should be prepared to help consumers evaluate the quality of information found online as well as recommend sites where credible information might be found. Obviously, these websites have sections to consumers that contain information presented in an easy language too understand by layperson. But, these sites are also useful for health professionals as source of information (common examples of sources are presented below).

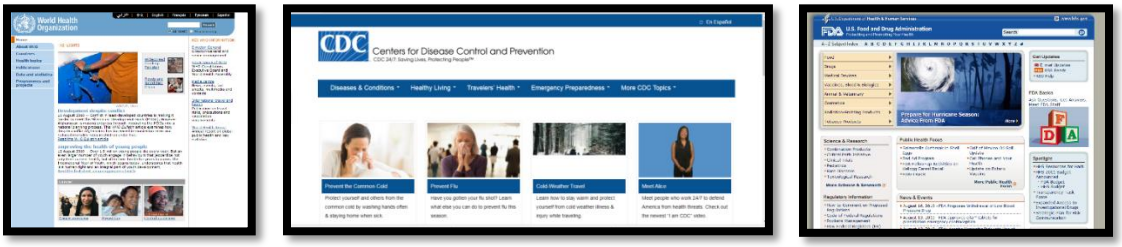


Figure 2.10 Common consumer health information sources

Table 2.5. Online Consumer Information Sources

Web Site URL	Maintained By	Contains Information About
http://www.nlm.nih.gov/medlineplus/	National Library of Medicine	Various medications as well as disease states and conditions.
http://www.fda.gov/cder/	Food and Drug Administration	New drugs, dietary supplements and recalls of drug or food.
http://www.gettingwell.com/	Thomson Healthcare	Variety of prescription drugs.
http://www.merckhomeedition.com/	Merck	Consumer based version of the Merck Manual. It includes a variety of interactive features.
http://www.healthfinder.gov/	Department of Health and Human Services	Variety of common medical conditions and diseases.
http://www.womenshealth.gov/ www.4woman.gov/	National Women's Health Information Center	Conditions and diseases of special interest to women.
http://www.cdc.gov/	Center for Disease Control and Prevention	Treatment and prevention of infectious diseases and listingof public health issues.
http://ods.od.nih.gov/	National Institute of Health	Compiles scientific information available about the efficacy and safety of dietary supplements.
http://nccam.nih.gov/	National Center for Complementary and Alternative Medicine	Resource describing ongoing research in the area of dietary supplements, and detailing efficacy information currently available.
http://www.safemedication.co m/	American Society of Health-System Pharmacists	Patient version of AHFS DI resource, as well as tips about medication administration and resources to empower patients to better manage their own health.
http://www.who.int/en/	United Nations	Information on outbreak, communicable and non-communicable diseases, etc.

2.5.3 Local Health Information Sources

When we are looking for programs, performance reports, and other information specific to Ethiopia, it is also good to look for some of the local websites. There are organizations that provide health and pharmaceutical related information in Ethiopia which some of the are listed below. However, searching their website might not be always successful in getting the required resources. Rather, it is always good to have contacts of experts in these organizations and when the need arise, information can be solicited/obtained about the resources needed.

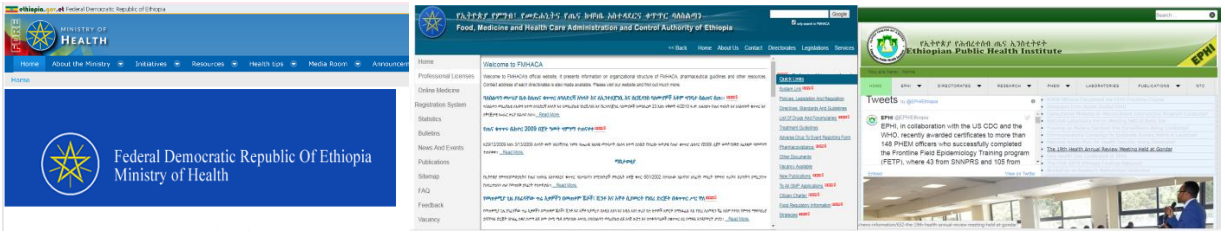


Figure 2.11. Local Health Information Sources

Table 2.6. Local Health Information Sources

Web Site URL	Maintained By	Contains Information About
http://www.moh.gov.et/cs/home	FMoH	Health care services, programs, documents & initiatives in the country.
http://www.fmhaca.gov.et/index.html	FMHACA	Food, medicine and health care services regulatory standards, inspection and licensing, product quality assessment and product registration requirements/documents.
http://www.pfsa.gov.et/	PFSA	National procurement, tender, forecasting and quantification and distribution of program and revolving drug fund pharmaceuticals.
https://www.ephi.gov.et/index.php	EPHI	National disease prevalence and surveillance, public health nutrition, laboratory services and public health researches.

2.5.4 Other Information Sources (Miscellaneous)

Occasionally, sufficient information to address a drug information request cannot be obtained from standard resources and may require the use of some alternative sources of information. For example, if a question involvesa recent news story reporting the removal of a medication from the market, a logical first place is to find initial information on the original news story. This can be done by searching various newswire services.

Table 2.7. Online News WireSources

News Source	URL
ABC	http://www.abcnews.go.com
AP (Associated Press)	http://www.ap.org
CBS	http://www.cbsnews.com
CNN	http://www.cnn.com
BBC	http://www.bbc.com
FDC Reports “The Pink Sheet”	http://www.healthnewsdaily.com/publications/the-pink-sheet
NBC	http://www.nbc.com
Reuters Health News	http://www.reutershealth.com
PR Newswire	http://www.prnewswire.com

Furthermore, in some cases, there may be limited information available. Hence, it would be wise to seek out an expert in the field. For example, when looking for recent recommendations regarding treatment of a specific disease state, it may be helpful to identify an organization affiliated with that disease state.

Additionally, when seeking information about a specific drug therapy, it may be helpful to contact the manufacturer or official agent to identify information available in-house. This resource could be especially helpful for obtaining difficult to access literature if a product is newly approved or for identifying a possible rare adverse drug reaction.

2.6 Guidelines as a source of information

Clinical practice guidelines are recommendations for optimizing patient care that are developed by systematically reviewing the evidence and assessing the benefits and harms of health care interventions. The quality of the evidence that forms the basis for recommendations is a key aspect

for interpretation and use of a practice guideline. Prior to selecting a clinical practice guideline for implementation in a health care system or for personal use by a health care professional, it is important that the quality of published guidelines be evaluated. There are different guidelines which are being used in various practice settings including diabetic care guidelines, asthma guideline, ART guideline, TB guideline, High blood pressure guideline, malaria guideline, etc,

Pharmacists' active involvement in preparation and implementation of evidence-based clinical practice guidelines is vital. A thorough understanding of evidence-based methodology will prepare the pharmacist to participate in this process. A DI pharmacist is an ideal person to help prepare and/or implement evidence-based clinical practice guidelines. He/she should use need to know how much confidence they can place in the recommendations while using clinical practice guidelines and other recommendations. There is a system for grading the quality of evidence and the strength of recommendations that can be applied across a wide range of interventions and contexts;

Table 2.8 Quality of evidence

1	▪ High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias ▪ Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias ▪ Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2	▪ High quality systematic reviews of case-control or cohort or studies ▪ High quality case-control or cohort studies with a very low risk of confounding, bias, or chanceand a high probability that the relationship is causal ▪ Well conducted case control or cohort studies with a low risk of confounding, bias, or chanceand a moderate probability that the relationship is causal ▪ Case control or cohort studies with a high risk of confounding, bias, or chance and a significantrisk that the relationship is not causal
3	▪ Non-analytic studies, e.g., case reports, case series
4	▪ Expert opinion

Table 2.9 Strength of recommendations

A	▪ At least one meta-analysis, systematic review, or RCT rated as 1, and directly applicable tothe target population; or ▪ A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 directly applicable to the target population, and demonstrating overall consistency of results
B	▪ A body of evidence including studies rated as 2, directly applicable to the target population,and demonstrating overall consistency of results; or ▪ Extrapolated evidence from studies rated as 1
C	▪ A body of evidence including studies rated as 2, directly applicable to the target populationand demonstrating overall consistency of results; or ▪ Extrapolated evidence from studies rated as 2
D	▪ Evidence level 3 or 4; or ▪ Extrapolated evidence from studies rated as 2

Chapter Summary

- There are three types of information resources in biomedical literature: primary, secondary, and tertiary resources.
- Tertiary resources provide information that has been filtered and summarized by an author or editor to provide a quick and easy summary of a topic.
- Secondary resources are mainly in the form of searchable database that enables location and retrieval of primary or tertiary resources.
- There are several types of publications considered primary, including controlled trials, cohort studies, case series, and case reports.
- Knowing the most appropriate resource for information retrieval is the first step in the provision of quality drug information.
- To perform a comprehensive search for an article, multiple resources must be used.
- Drug or health information retrieved from Internet-based or online media needs to be evaluated for its accuracy, comprehensiveness, and recent update.

Chapter Three: Managing Drug Information Queries

Chapter Description: This chapter enables the participants toapply organized and structured approach while receiving medicine information requests and formulating effective responses and recommendations.

Chapter Objective: At the end of this chapter the participants will be able tomanage medicine information queries properly.

Enabling Objectives: At the end of this chapter, participants will be able to:-

- Demonstrate the systematic approach to answer DI queries
- Formulate responses and recommendations

Chapter Outline:

This chapter has the following outlines:

- Introduction
- Step-wise approach in responding to DI queries

Allocated Time:180 minutes

3.1 Introduction

Drug Information Pharmacists are expected to provide, as a core function of the DIS, accurate, complete and timely response to the enquiries coming from health care providers, clients/patients and the general public. In order to provide meaningful responses and effective recommendations to these drug information questions, assumptions/perceptions that may compromise the relevance of the response must be dealt with. One such instance is the false perception that many drug information questions do not pertain to specific patients. Another is the perception that the seemingly casual interactions with requestors and the lack of formal, written consultation somehow do not necessitate the need for in-depth analysis and extensive involvement in patient management.

On the same token, the absence of sufficient background information and pertinent patient data can greatly impair the process of information synthesis and the ability to formulate effective responses.

Therefore, a systematic approach that enables the capture of pertinent background data, and outlines a sequential method of elucidating the query, is of utmost importance.

Advantages of following a step-wise approach to respond drug information queries

- It helps to understand the context of the query and provide the right kind/amount of information
- It helps to understand the scope of the query to focus on the right response
- It helps to provide credible information
- It facilitates smooth and clear communication with healthcare professionals and patients

3.2 Step-wise approach in responding to drug information queries

Activity 3.1 Points for refelection on steps in responding DI queries

"What steps would you follow to respond to a drug information query?"

The following step-wise approach is recommended to respond drug information queries.

Step 1: Secure Demographics of Requestor

Step 2: Obtain Background Information

Step 3: Determine and Categorize the Ultimate Question

Step 4: Develop Strategy and Conduct Search

Step 5: Perform Evaluation, Analysis, and Synthesis

Step 6: Formulate and Provide Response

Step 7: Conduct Follow-Up and Documentation

Step 1: Secure Demographics of Requestor

The requestor's "profession" (e.g., physician, pharmacist, nurse, lay person) should indicate educational experience and knowledge base; therefore, the individual receiving the query can use this information to determine the appropriate mannerism (in terms of educational level) to formulate and deliver the response.

Although the presentation of the initial question provides insight to the requestor's sophistication and knowledge regarding the subject matter, it is important to more directly determine the requestor's position, training, and anticipated knowledge. The requester's name, age, location, affiliation (institution or practice if he/she is health care provider) and frame of reference (title, profession or occupation and rank) are among the key information secured. Moreover, it is essential to secure a mechanism for delivery of the response such as telephone number(s), fax number, and/or address (mail or e-mail) or location, and so forth.

Step 2: Obtain Background Information

Obtaining background information to develop a more complete picture of the question is essential to effectively respond to drug information enquiries.

General Questions for Obtaining Background Information

- Whether the request is patient specific or academic
- The resources that the requestor already consulted
- If the query is patient specific,
    - information regarding diagnosis,
    - specific patient laboratory values
    - other medications, and pertinent medical information
- The urgency of the request (i.e., negotiate the time

Some requesters may have referred resources for their query prior to consulting the DI Pharmacist. It's therefore useful to know which resources were checked to avoid duplication of effort.

The responder may also be expected to respond to intermediaries- any person involved in the process that is not truly the end user of the response- which may include medical students, nurses, pharmacists, and administrators' assistants. In dealing with these intermediaries, one must decide to work with them (i.e., educate them concerning the information needed and why it is needed) or bypass them (i.e., interact with the end user of the information directly). One should not allow an intermediary with incomplete or inaccurate background information to drive the consultative process.

Thus, when the aforementioned background questions are utilized appropriately, the response to information requests is very efficient.

Appropriate communication principles should be followed during the process of securing any type of information from the requester. Phone conversations may seem less vulnerable to communication mistakes but often the tone and manner as well as the phrases used in addressing a requester give away the professional's overall performance as a good communicator. Appropriate wording, tone and manner must be exercised whether the requester is posing a question over the phone or in person.

Step 3: Determine and Categorize the Ultimate Question

Determination

Once the background information is obtained with an open and productive exchange with the requester, the channel from receiving to responding a query will be through identifying and categorizing the ultimate question from the requester's perspective. The present step majorly relies on the adequacy of pieces of background information obtained to form the ultimate question.

The ultimate may essentially be the same as the original question, particularly if the question is truly not patient specific.

Categorization

Categorization is useful not only for the initial development of the search strategy, but also for the determination of resources. Classification of a request aids in developing a more effective search strategy, decreasing the time requirement and increasing the accuracy of the response.

Table 3.1 Examples of Drug Information Categories

Examples of Drug Information Categories	
• Adverse Effects	• Identification of a product
• Availability	• Pharmacokinetics
• Compatibility/Stability	• Pharmacology
• Compounding	• Poisoning/Toxicology
• Dosing and Administration	• Pregnancy and Lactation
• Drug Interaction	• Therapeutic Use

Step 4: Develop Strategy and Conduct Search

The significance of the earlier step was to guide on the list of specific resources selected. Prioritizing these resources based on their probability of containing the desired data or information will help in pin-pointing the response.

The desired information is then collected from each of the sources. List of commonly used drug information resources categorized by type of drug information is annexed in 2.1.

So as to conduct search, the three types of information sources in the literature hierarchy (discussed in Chapter 2); primary, secondary and tertiary information sources, may be used.

It is best to follow an organized, stepwise approach when searching the drug information literature. This process involves a search that starts with the tertiary literature, followed by the secondary literature and then to the primary resources.

Step 5: Perform Evaluation, Analysis, and Synthesis

At this step, the information retrieved must be objectively critiqued. DI provider should take time to evaluate the information, analyze it, and then synthesize it into a good reply.

Evaluation

Evaluating the quality of the information is key to a good response. Drug literature evaluation skills (basic understanding of biostatistics and research methodology and skills in the critical evaluation and application of biomedical literature), become critical.

Analysis

Analysis of the found information must be done with the requestor demographics in mind and the category of the question to ensure that the answer formulated will be useful and relevant. It involves separating the information into its isolated parts, so that each can be critically assessed, and thoughtful review and evaluation of the weight of available evidence.

Synthesis

Synthesis is the careful, systematic and orderly process of combining or blending varied and diverse elements, ideas, or factors into a coherent response. As it relates to pharmacotherapy, synthesis involves the careful integration of critical information about the patient, disease, and medication along with pertinent background information to arrive at a judgment or conclusion.

Step 6: Formulate and Provide Response

Despite the setting or circumstances, the formulated response must be to the point, yet adequately comprehensive. An effective response must answer the question. In addition, response to a question must be timely, current, accurate, complete, concise, well referenced, clear and logical, objective and balanced, free of bias or flaws, applicable to specific circumstances, answers important related questions and addresses specific management of patients or situations.

Formulating a response comprises a series of steps that must be performed completely, objectively, and in a logical sequence. It requires the use of a structured, organized approach whereby critical factors are systematically considered and thoughtfully evaluated. The steps in the process include assembling and organizing a database of the patient information, gathering information about relevant disease states, collecting medication information, obtaining pertinent background information, and identifying other relevant factors and unique or special circumstances.

The response to a question must include a restatement of the request and clear identification of the problems, issues and circumstances. The response should begin with an introduction to the topic and systematically present the specific findings. The introduction should provide a comprehensive but concise review of the disease, drug, or situation proposed in the question.

The body of the answer, which constitutes a review of the pertinent literature that answers the question, should follow the introduction. The literatures consulted should be reviewed and discussed here and any controversy or debate among the studies should be addressed. The studies should be appropriately cited in the reference section of the response form to minimize plagiarism.

Conclusions and recommendations should give a brief synopsis of the information provided and should usually include a professional opinion based on the literature cited. If literature contains conflicting data that must be presented to the requestor, a logical argument should be supplied. Specific recommendations must be scientifically sound and clearly justified.

The requester might choose getting the response verbally, via telephone or over a physical conversation. In such instances, the formulated response must be delivered in the appropriate manner which considers proper and formal wording, calm but clear manner of speech and addressing the important point/conclusion of the response.

Case Study 3.1 Paired exercise on steps in responding DI queries	
 .	Dr. A.G. is an Emergency Medicine resident. He came to you (Drug Information Pharmacist) today to enquire on any possible drug interaction between Enalapril, Atorvastatin, Allopurinol, Prednisolone, and Ibuprofen. Upon your request, he discloses that these medications are being taken by a 50-year-old, male, 65kg patient who has hypertension, hyperlipidemia, gout arthritis and radiculopathy. He requires a hard-copy of the response within 3 hours. He also needs print out of resources consulted.
Instructions: - ***Use the information above to follow the 7 steps and formulate a response.*** - ***Describe each step-in relation to the case.*** - ***Use the request and response forms (Annex 3.1 and 3.2) to fill out the proper information for documentation.***	

Step 7: Conduct Follow-Up, Follow-Through, Documentation and Reporting

Follow-up is the process of verifying the appropriateness, correctness, and completeness of a response following the communication. Follow-through is the process of readdressing a request based on the availability of new data or change in the situation or circumstances that were decisive factors in the synthesis of a response.

Thorough documentation is essential for reducing liability and potentially promoting the development of a continual service. At a minimum, the ultimate question, the materials searched, the response, and follow-up (or follow-through) should be documented.(Annex 3.1-3.3 and 9.1)

Follow-up allows you to know if your recommendations are accepted and promptly implemented. Also, it is a characteristic of a true professional and demonstrates the pharmacist's commitment to patient care. Furthermore, follow-up is required for outcome assessment and, when necessary, to reevaluate the recommendations and make appropriate modifications. Finally, follow-up allows pharmacists to receive valuable feedback from other requesters and to learn from the experience. The activities to be executed include the following:

1. Perform follow-up on the outcome of the information provided either through telephone surveys, physically or by using a standard feedback form (Annex 4) so as to determine:
    a. The outcome
    b. Relevance of the information provided
    c. If additional information is required
2. Reconsider the quality of information provided if the requestor is not satisfied with your response.
3. Use the data obtained in the feedback form for quality assurance purpose.
4. Document all enquiries and responses.
5. Produce statistics each year

Documentation is necessary for follow-up, quality assessment and other performance improvement and management activities. The contents of a proper documentation and reporting are discussed in more detail in Chapter 9.

Case Study 3.2: Paired discussion *on step-wise approach*	
	**Initial question-** *Can ranitidine cause thrombocytopenia (platelet count of less than 150,000mm^3)?*

1. **What would beyour response in the absence of relevant background information?**
2. **What would be the potential response if the following pertinent background information and patient factors provided?**

Pertinent background information

The requestor is a physician who is evaluating a patient for suspected Cushing disease. The patient has been hospitalized for 8 days and has undergone extensive diagnostic tests, including serial blood sampling to establish the diagnosis. Over the last 4 days, the patient has experienced a rapid decline in her platelet count. The physician is aware that cimetidine can cause thrombocytopenia.

Her patient is taking ranitidine, and she would like to know if the thrombocytopenia could be induced by this medication.

Pertinent patient factors

L.B. is a 38-year-old obese woman with Type 2 diabetes who is being evaluated for Cushing disease.

Past Medical History

- Gastroesophageal reflux disease (GERD) × 6 years
- Type 2 diabetes × 1 year

Social History

- No alcohol use
- No tobacco use
- No occupational or environmental exposures

Current Medications

- Ranitidine 150 mg orally twice a day (intermittently for 6 years)
- Metformin 500 mg orally three times a day (for about 8 months)
- Heparin 100 USP units/mL (as needed for flushing heparin lock)
- No complementary/alternative or nonprescription medications

Allergies/Intolerances

- Penicillin (rash)

Laboratory Results

Sodium 137 mmol/L, potassium 4.9 mmol/L, chloride 102 mmol/L, CO_2 24 mmol/L, creatinine 0.9 mg/dL, glucose 133 mg/dL, BUN 12 mg/dL, albumin 3.4 g/dL, calcium 2.35 mmol/L, magnesium 0.81 mmol/L, phosphorus 3.8 mg/dL, LFTs within normal limits, WBCs 5.6×10^9/L

Date	Platelet Count
1/17	241 K/mm^3
4/20	230 K/mm^3
4/24	212 K/mm^3
4/25	159 K/mm^3
4/26	114 K/mm^3
4/27	97 K/mm^3
4/28	81 K/mm^3

Instruction: answer the following questions based on the above background and pertinent patient factors information.

Disease factors	Which disease factors could be considered in L.B.'s case? In terms of progression of the condition, etc.?
Medication factors	Which medications could possibly bring about the condition?
Analysis and synthesis	Analyze the factors identified to pin-point the cause of the condition?
Response and recommendations	Identify the most-likely culprit for the condition and formulate a response the question in the manner it was presented.
Case message	• Was there any difference between answering the query in the absence and presence of background information? • Could you comment on the consequences of having to give the response without the collection of pertinent clinical data?

The flow of enquiry and stepwise approach in answering drug information is summarized below

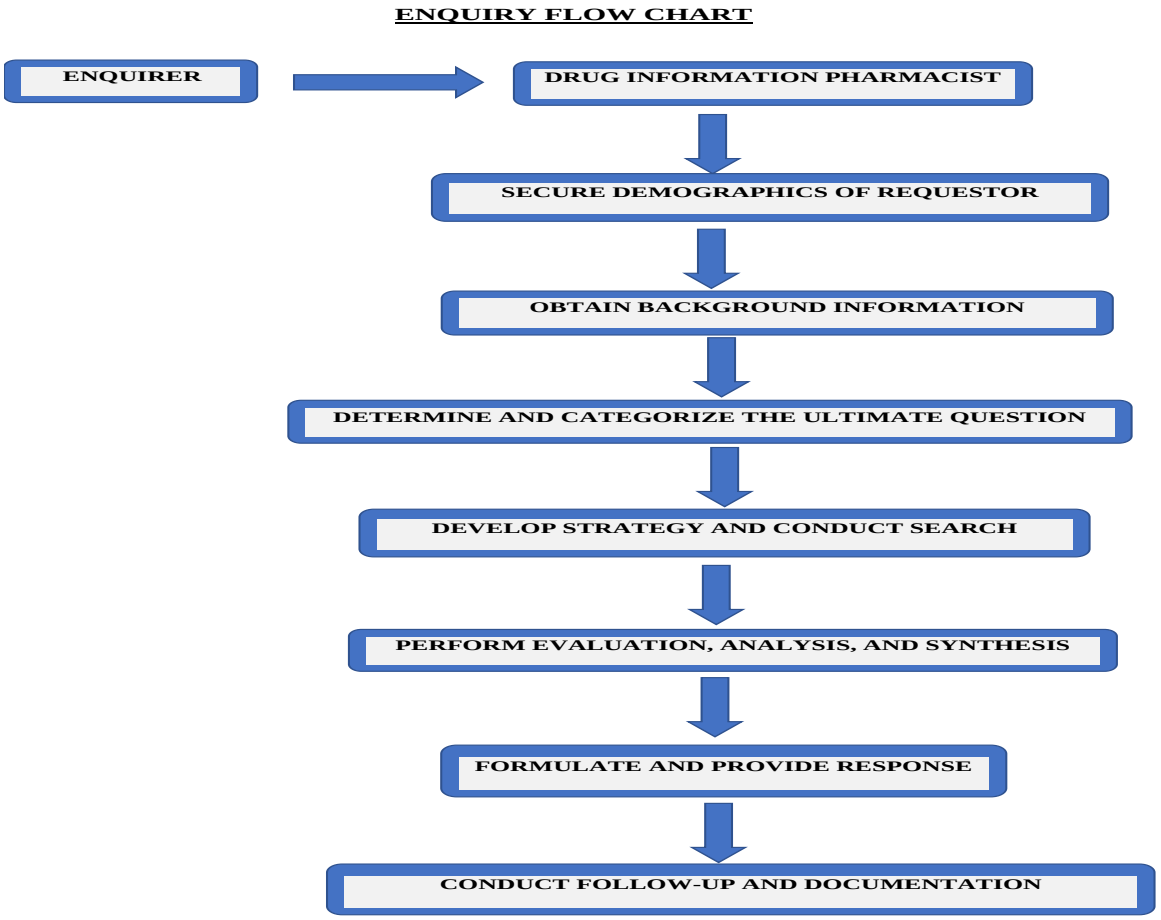


Figure 3.1 flow of enquiry

Chapter Summary

- The absence of sufficient background information can greatly impair the process of information synthesis and the ability to formulate effective responses.
- A systematic approach that enables the capture of pertinent background data, and outlines a sequential method of elucidating the query, is of utmost importance.
- Formulating a response comprises a series of steps that must be performed completely, objectively, and in a logical sequence.

Chapter Four: Production and Dissemination of Medicine Related Information

Chapter Description: This chapter enables the participants toknow the principles that guide a professional writingin preparing and disseminating common medicine-related information materials.

Chapter Objective: By the end of this chapter, participants will be able toprepare and disseminate medicine and health related information to healthcare providers and other clients.

Enabling Objectives: By the end of this chapter, participants will be able to:

- Identify steps in professional writing
- Prepare medicine information materials
- Disseminate medicine information materials

Chapter Outline:

This chapter has the following outlines:

- Professional writing
- Preparation of medicine information materials
- Dissemination of medicine information materials

Allocated Time:195 minutes

4.1.Professional writing

4.1.1 Introduction

Professional writing is a style of written communication used in a workplace environment that allows professionals to make informed decisions. Professional writing typically has a formal tone and differs from written text that is considered literary or artistic. In a professional writing although the format changes the general principles remain the same. Therefore, though the objective varies, a healthcare provider must know how to write professionally.

There are, generally, four larger purposes for the existence of written materials. These are: inform, instruct, persuade, or entertain. The first three items are those usually considered in a professional writing, although including the fourth, whenever possible, will help convince people to read what has been written.

4.1.2. Steps of professional writing

Preparation:

- **Know the purpose:**The initial step in writing is to know the purpose, why something needs to be written in the first place. Here, it is necessary to have a good idea of the expected endpoint.
- **Know the audience:**Before the first word is written, it is necessary to know the audience, which involves knowing the type of person who will be reading the final document and where it will be published. It is necessary to aim both the writing style and depth of information toward the audience (see writing style below). If something is written for physicians, it is not likely to be understood by lay people. In addition, it is appropriate to have a secondary audience in mind. For example, a report written for physicians may be of interest to pharmacists or nurses. However, make sure the secondary audience is not served at the expense of the primary audience.
- **Synthesize the medicine information:**Synthesis means to combine a number of different pieces of drug information into a whole. Synthesis involves concisely summarizing and linking the different information sources in order to review the literature on a topic, provide recommendations, and connect practice to the research. Synthesis usually goes together with analysis because you break down a concept/idea into its important parts/points (analysis), so you can draw useful conclusions or make decisions about the topic or problem (synthesis).

  Synthesis determines:

- Which sources overlap or share the same opinion/findings?
- Are there any common traits or themes in the information sources?
- What meaning, or conclusions can be drawn from the pieces of information on the topic?
- How might that new meaning change or reinforce the practice/the question at hand?
- Is the piece of research/information source weak or strong?
- Using the statistics, facts, or knowledge in the research, what kind of story have you crafted for the reader? What is your angle or your personal interpretation of the evidence?
- How have you shown the reader which parts of the argument (or which pieces of research) are most useful or most important?

Writing the material:

- Once the preparation is completed, the writing can begin. Unfortunately, there is no easy way to learn how to write professionally; it just requires a lot of practice. However, several rules can be followed to make your writing professional. For the components to be included while writing. (Annex 4.1).

Review the information:

The importance of reviewing the information to be published by professionals other than the professional who prepared it, is obvious. Before dissemination, it is recommended that the prepared material is first revised for completeness, flow, and relevance. It could be colleagues, seniors or fellow Pharmacists involved in Pharmacy service activities who could be asked to go over the information. Mistakes that are of minor or major importance could be caught in time, before reaching the intended audience. But, the DI Pharmacist should assume responsibility for content of the information provided in the material. In line with this, a disclaimer note should be added indicating that no legal responsibility is claimed on the person/unit who prepared the information, if the information is applied directly to patients/clients.

4.1.3 Styles of professional writing and sections of a typical document

There are three types of writing styles commonly used by healthcare professionals. These are pure technical style, middle technical style, and popular technical style.

Pure technical style:is used by business or technical professionals when they are writing for other professionals in the same or similar fields. The great majority of writing done by health professionals will be in this style, because it is usually other health professionals who will be reading their work. For example, an article published in journals like the Ethiopian Pharmaceutical Journal, Ethiopian Journal of Health Development, Ethiopian Medical Journal, etc. The authors can use technical jargon, because they can expect the readers to understand it. It is also written in formal English.

Middle technical style: is very closely related to pure technical style. Authors use this style when they are writing for readers with a variety of technical backgrounds, with everyone having some unifying factor. For example, a report regarding a hospital's medication error reports might be presented to the hospital's Drug and Therapeutics Committee. Although each has a background that rationalizes their membership, not all of them would understand the specific event happened. Therefore, it is necessary to better explain, or sometimes avoid, some technical areas or specific abbreviations. Otherwise, this writing style is very similar in most respects to pure technical style.

Popular technical style: is used in anything meant for the public. Common language is used throughout. For example, a patient information sheet would need to be written in this style.

Activty 4.1 Paired discussion on components of typical document	
	What are the components of a typical document?

In professional writing, it is recommended to include the three parts of a typical document- Introduction, Body, and Conclusion. However, in cases of a clinical studies, the author can take a different format to include Introduction, Methods, Results, and Discussion (IMRAD) sections.

Introduction part: thispart is designed as a road map to inform the reader what they can expect in the rest of the document. The introduction should state a clear objective about the document. It’s expected to be short, containing and maintaining a clear and concise content and format. The introduction should generally not be a conclusion as many people will read no further, making the remainder of the document a waste of time and effort. Hence, in the introduction, start out strong, to encourage the reader continue reading.

The body: the bodypart: contains all the details. In a research article, the body may be divided into the methods, results, and, possibly, discussion sections, although the latter section may be incorporated into the conclusion**.** Many rules can be followed in preparing the body of a document.

- Be concise yet include all the necessary information. But, avoid unsupported bias.
- Cover the information in a logical order, so that it flows easily from one point to another.
- Material that can identify patients should be left out.
- Writers should also put the information in their own words, by doing so, they demonstrate they understand the topic and it becomes concise.
- Proper citing and referencing should be included in the body to give credit and avoid plagiarism. However, avoid too much quotation while bringing wordings directly from another work.

Conclusion: the conclusion should be placed at the end of the body of the document. This conclusion should follow logically from the information presented and should serve to summarize that information. It should also correspond with the objective stated in the introduction. A common mistake is to write the conclusion in a general manner, rather than addressing the specific issue or patient in question, which is what the reader wants to hear about. The readers need something to bring their thoughts together at the end, and the author is in the perfect position to provide this closure. However, the author should also be careful to avoid extrapolating beyond the information available.

4.2.Preparation of specific medicine information materials

Introduction

Drug information services should be involved in preparation and dissemination of drug information in the form of brochures, fliers, posters, bulletins, leaflets, newsletters, drug inclusions/exclusions, drug alerts etc… to health care providers and patients/communityin a language appropriate to users. These informational materials can be prepared in both print and electronic form. The information should be current, evidence based (objective), unbiased and well referenced.

Newsletters

Newsletters, whether printed or electronic have been a part of any pharmacy practice, most frequently in hospitals as a method for communicating DTC actions and other drug-related topics to

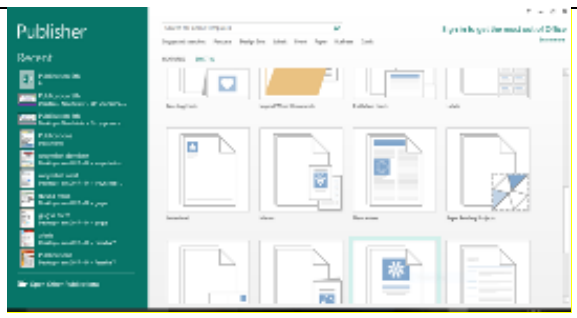
the medical, pharmacy, nursing, and other health care provider staffs. Nowadays, the electronic versions of newsletters can provide direct links to further information and even such benefits as videos.

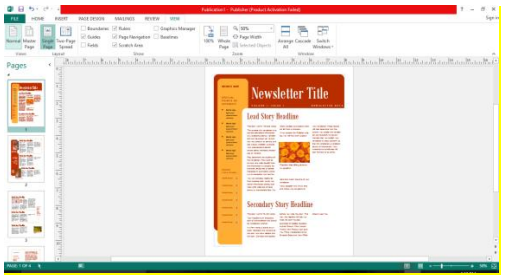
The production of newsletters, whether printed or electronic, follows the same basic steps:

- *Defining the audience*- who will, or at least should, be reading the newsletter or accessing the contents.
- *Defining the Goals*- the goal generally includes informing and educating the reader, and to report news.
- *Identifying Constraints*-
    - *Time:* It is necessary to have time to write, edit, and perform other functions in publishing the newsletter to get the finished result to the printer, so that it can be ready for distribution on time.
    - *Manpower*-: Generally, there are two extremely hard parts to publishing a newsletter or website, neither of which is the actual writing. One of them is coming up with topic ideas; the other is to make it look good. If a group of dependable people are willing to work together to make sure the articles get written, the job may be easier.
    - *Resources:* Best to keep these in mind to decide on the mode of delivery: printed newsletter vs. group emails. Money may not be a direct issue but often allocation of adequate finance for DIS in a typical Health Facility would lead to limited resources like paper, printer, etc which could be used to duplicate and disseminate the information.
- *Determine the appearance:* -While it might be easy to believe substance is more important than appearance, it eventually becomes noticeable that many people do not bother looking at the substance if the appearance is poor or unprofessional. Therefore, one of the most important things is to make the publication look appealing.
- *Deciding the content:* - Content wise, coming up with new ideas on a regular basis can be rather difficult. A newsletter or website can be used for a range of information; a list of possible areas is included (Annex 4.2). If possible, material that was prepared for a different audience can be recycled for the newsletter or website readers. For example, material from the DTC meeting might be turned into a short review of a drug. Whenever possible, the material presented should be focused on topics not available to the audience from another source.

Tips: note the following additional points while preparing Newsletters.
▪ Be consistent: - a newsletter should have its own style that is recognizable by the reader, and that the various pages must fit with one another. The easiest way to do this, with either a newsletter or website, is to create a template, style sheet, or theme to be used throughout. ▪ Use appropriate software and equipment: - a high-end word processor or desktop publishing program and a laser printer can be used. ▪ Make the newsletter look good: - Use white space properly and don't just crowd in as much material as possible on the page. The reader will have a hard time following if it is too crowded and may just give up. • Design a mast head: - it's is essentially the part of the first page of the newsletter that gives the name of the publication, volume, issue, date, and so on, which may be at the top of the page or down one side of the first page.
Fliers and brochures follow the same guiding principles as preparing newsletters while Therapy Updates, Drug alerts and Abstracts could be considered specific publishing names or areas as contents of a newsletter.

SOP for the preparation of a typical newsletter using Microsoft publisher

Step	Activity	Result
1	Go to start---→Open Microsoft Publisher	
2	Click newsletter to show the different templates from new versus classic designs.	

3	choose a desired template from the built in templates as per the content you would like to develop, from the options given under the Newsletter section.	
4	As an example, the following template is chosen	
5	Edit the contents and formats as per your preference to prepare own material	

Activity 4.2 paired exercise to prepare newsletter

Prepare a one pager newsletter on a current issue of your choice and apply the lessons you learned to make it relevant and appealing.

While preparing the newsletter and similar information material, be sure that the information meets the following criteria:

Appearance	• Color-mix and contrast • Use of pictures (relevance, position, etc.) • Use of space (congested vs. enough white space)
Substance of the message	• Objective • Unbiased • Current • Availability and quality of reference • Flow of information
Components of the newsletter	• Vol, issue #, date • Title (concise and catchy • Use of left column • Availability of appropriate sections • Disclaimer • Address of DIS/editors

A sample of drug alert is provided in Annex 4.3 and a sample newsletter is provided in Annex 4.4.

Monograph

A rational evaluation of all aspects of a drug in relation to similar agents provides the most effective and evidence-based method in deciding which drug is appropriate for formulary addition. *The drug evaluation monograph provides a structured method to review the major features of a drug product*. Once it's prepared, it can easily be used as a structured template or overview of a drug product that allows for easy comparison or contrast to other products that may be used for the same indication or that are in the same product class.

A monograph contains pertinent drug-specific information and is a powerful tool for the pharmacy to guide the rational development of a drug formulary. While monograph preparation can be very time consuming, it is extremely important and should be given proper attention. The structured evaluation process of a drug monograph, in many cases, is the only time a full, fair, and balanced review of a drug that may be presented to a practitioner.

Commercially prepared monographs can be obtained from several sources and can be used as it is or with modifications to suit the needs of the institution. But be aware that the quality of the commercial monographs may vary, and they may need extensive updating. Often, writing a new drug evaluation monograph may be easier than improving a commercial monograph.

Pharmacists have a unique role in the preparation of a monograph in that they view the drug product from a whole and macroeconomic aspect. Whereas, often prescribers use, and misuse of a product may be based on information presented on a single study, package insert, pharmaceutical representative information, or some other microeconomic aspect of a drug product that may or may not represent the full utility of the drug product. The precise monograph should be tailored to the institution, patient population, clinic, so on.

The basic format to follow during the preparation of a monograph is provided in Annex 4.5 and sample monographs in Annex 4.6 and 4.7.

Case Study 4.2 Writing a monograph on a medicine	
	A physician working in Internal Medicine would like to get information on Imipramine and asked the DI Pharmacist to furnish summarized information.
	Instruction: Write a one pager monograph on imipramine.

4.3.Dissemination of medicine information

All the work done in preparing newsletters would be for nothing if the readers do not get the newsletter. A good distribution system must be developed. Sometimes it can be as simple as posting them on notice boards, but electronic systems are often used to reach wider audiences and they have the added advantage of direct feedback from the recipients.

A good distribution system must be developed for published DI materials. It is important to make sure the readers get the materials. Ensure readers get the materials on a regular "cycle," so that they know when to anticipate the arrival of the publication. Consider making the material available on the Internet. Text documents, such as posters, are easily placed on a website. Full slide presentations can be placed on a website, using streaming audiovisual.

Chapter Summary:

- Professional writing is a skill necessary for every health professional.
- Newsletters, drug alerts, and monographs are common DI materials.
- Knowing the audience and keeping written items clear, concise, complete, correct, and in the appropriate format will ensure proper information dissemination.
- All the work done in preparing newsletters would be for nothing if the readers do not get the newsletter.

Chapter Five: Medicine Use Education and Continuing Pharmacy Education

Chapter Description: This chapter provides a general guide onmedicine use educationto clients, continuing pharmacy education and effective communication with patients and health care providers.

Chapter Objectives: By the end of this chapter, participants will be able to:provide medicine use education to clients and continuing pharmacy education to health care providers.

Enabling Objectives: By the end of this chapter, participants will be able to:

- Provide medicine use education.
- Design and organize continuing pharmacy educationevents.
- Describe approaches to communicating with health care providers and patients.

Chapter Outline:

This chapter has the following outlines:

- Medicine use education
- Continuing Pharmacy Education
- Effective communication with patients/clients and health care providers

Allocated Time:135 minutes

5.1 Medicine Use Education

5.1.1 Basic principles of medicine use education:

Empowering clients on proper use of medicines through patient education is essential to improve treatment outcome. Accordingly, community education in general and patient's education in the waiting areas in particular have paramount importance and sustainable effect.

Principles to guide public education should include the following:

- Public education should address important drug use issues with special focus on rational use of medicines.
- Public education should encourage informed decision-making and cover basic concepts of medicine use, like: -
    - How to choose when to self-medicate and when to seek medical advice,
    - Which conditions that do not require medication,
    - How to read a drug label or patient information.
- Public education on medicines should recognize and consider the cultural diversity and the influence of social factors.
- Public education should have clear and measurable objectives. To change deep-rooted beliefs and practices, itrequires a sustained effort and a stepwise process which moves from creating awareness, to acquiring knowledge and finally changing behavior.

5.1.2 Phases of organizing medicine use education

Preparatory phase:

Before providing medication use education, the following points should be addressed.

- Perform needs assessment which helps to identify possible gaps and will guide content development and delivery
- Prepare well-structured patient education material on proper use of medicines. Sample patient education materials is annexed. (Annex 5.1).
- Communicate and engage the appropriate unit /department on the selected topic.
- Get well prepared on the selected topic.

- Identify convenient location to conduct medicines use education; this may be at the patients waiting areas.
- Decide on ideal time for medicines use education. This might be early in the morning during patient waiting time.
- Consider socio-cultural aspects of the audience. Identify and familiarize oneself on common myths and facts on the selected topic.

Medicine use education session

During medicine use education session

- Introduce yourself
- Explain the objective of the day's session
- Respect clients and be supportive,
- Make it interactive.
- Always encourage clients to raise questions regarding medicines use. Acknowledge questions; remember there is no simple or non-sense questions, it is only the way we see it.
- Ask some questions at the end of the session.
- Summarize major points of the session.

Post event phase

After conducting medicine use education, recording, documenting and reporting is crucial. Use the following recording form to record and document medicine use education conducted.

Table 5.1. Recording form for medicines use education to clients at health facilities

Name of the facility:_____

No	Date	Time		Specific topics covered	Issues raised by attendees	attendees		Location /target*	Name and profession of educator	Remarks
		Start	End			F	M			
1										
2										
3										
4										
5										

6										

*who were the targets such as diabetes, hypertension, mental health, gyn/obs,TB/HIV, general OPD etc.

While recording medicine use activities make sure the following key milestones are properly noted and recorded.

- Date of the event
- Time (both start and end)
- Specific topics presented/discussed (title of the education)
- Key issues discussed which require further attention
- Number of participants (Male/female from which total will be summed)
- Location/Venue where the event is conducted
- Name and profession of the presenter/educator
- Remark

The medicine use education record is summed and be reported every month, quarter, bi annual and annually along with other DIS activities using DIS reporting format that will be discussed in Chapter 9.

Activity 5.1 Group exercise on medicine use eductaion	
	You are assigned to organize a 20 minutes medicine use education on AMR to be presented to patients/clients on April 27, at the waiting area of hospital's OPD.
Instruction/question:Prepare medicine use education material on AMR and conduct medicine use education to clients.	

5.2 Continuing Pharmacy Education (CPE)

5.2.1. Introduction

Continuing Pharmacy Education (CPE): a structured process of education designed or intended to support the continuing development of pharmacists and other members of the pharmacy workforce to maintain and enhance their professional competence. A CPE activity shouldpromote problem-solving and critical thinking and be applicable to the practice of pharmacy.

As the health care environment undergoes rapid transformation, increasing costs paired with technological advancements have highlighted the need for value-based health care services and innovative modes of delivery. Simultaneously, the role of the pharmacist is undergoing

transformation;extends from preparing and dispensing of product to all-encompassing pharmaceutical care responsibilities.

Currently pharmacy graduates are expected to engage in direct patient care roles (through collaborative practice, perform comprehensive medication management, and provide preventative care services). With these transformations, expectations for ensuring competence have grown. To meet this and future challenges, the drug information pharmacists must be prepared to provide continuous pharmacy education for pharmacy professionals in order to adequately deliver quality health care.

Benefits of continuing pharmacy educationincludes:

- It enables pharmacy professionals to be competent in managing practicalchallenges;
- It updates pharmacy professionals on recent developments in different areas of the profession;
- It ensures optimal medication therapy outcomes and patient safety;
- It satisfies the educational requirements of pharmacy professionals.
- It enhances the capacity of pharmacy professionals in delivering quality care for their patients.

The design of CPE activity can be either knowledge based or practical based:

- Knowledge-based CPE activity**:** designed primarily for professionals to acquire scientific knowledge.
- Practice-based CPE activity**:** primarilydesigned to systematically acquire specific knowledge, skills, attitudes that expand or enhance performance behavior.

5.2.2 Organizing CPE events

The DI pharmacist organizes trainings for health care providers on different aspects of pharmacy practice to enhance their professional competence. Before organizing CPE event, training needs assessment shall be conducted to identify possible gaps and should guide content development and delivery. A needs assessment should employ multiple strategies to identify the specific gaps in knowledge or skills or areas for enhancement. The DI pharmacist should identify gaps between what pharmacy professionals do and what is needed and desired in practice. Strategies for needs assessment should incorporate a method or methods in which representatives of the intended audience participate in identifying their own continuing education needs.

Once the specific gaps for enhancementare identified, it is important to designing and organizing in-service training programs. The following steps are involved in organizing training programs:

1. Identify training needs of health care providers through training need assessment.
2. Identify relevant training topics to be addressed.
3. Decide on the mode of delivery based on target audience and topic of training.
4. Identify trainers.
5. Develop training materials.
6. Develop detailed training program and cost breakdown.
7. Secure finance to cover the training expenses.
8. Conduct training using Adult Learning Technique.
9. Prepare training report and communicate it to the health facility management and concerned bodies.
10. Monitor and evaluate training programs through audience feedback, survey, end of training evaluations and event observations.

As discussed in the medicine use education above, every CPE event should be recorded, documented and reported.

Activity 5.2: Excercise on recording medicine use education data

On January 12, 2018, you organized and conducted a medicine use education on Self-medication starting at 8:30 am for 20 minutes for 45 persons of whom 12 were female. A week after the previous medicine use education, another medicine use education on medicine sharing was organized and presented by Mr Taye, a Pharmacist, which started at 8:45 am for 25 minutes for 39 (22 female) persons. On January 28, 2018 you organized CPE seminar presented by Dr. Ketsela on new medicine for the treatment of diabetes to 50 (19 female) of your facility staff starting from 3:00 pm - 3:55pm.

Instruction/question: *Record the data given in the recording form (Use table 5.1 above)*

5.3 Effective Communication with patients/clients and Healthcare Providers

5.3.1 Effective communication with patients/clients

Communication is effective when patients receive accurate, timely, complete, and unambiguous messages from pharmacists in ways that enable them to participate responsibly in their care. The

communication process between pharmacists and patients aims toestablish an ongoing relationship between the pharmacist and the patient, facilitate the exchange of information necessary to assess a patient's health condition,implement treatment of medical problems, and evaluate the effects of treatment on apatient's quality of life.

Medication Use Education Tips

- ✓ Have a good eye contact and audible voice
- ✓ Move around and watch your body language
- ✓ Read your audience
- ✓ Try not to read your presentation
- ✓ Never ever turn your back to the audience
- ✓ Communicate in three ways: hearing, sight, hands on participation
- ✓ Let audience speak
- ✓ Use the word "we" to include the audience
- ✓ Remember the three T's: tell the audience what you are going to tell them, tell them, and tell them what you have just told them!!

A DI pharmacist can track effectiveness of communication using the following techniques.

- o Clients will attentively follow your education.
- o Clients will raise queries and questions.
- o Clients will respond the questions you may raise.

5.3.2. Effective communication with health care providers

Poor communication with the healthcare team leads to frustration and lack of interest between professionals as well as compromise patient care.To communicate effectively, the DIS personnelmust be comfortable with their role on the health care team and confident in their contributions to patient care.TheDI pharmacist should stay up to date within his/her area of expertise.

Tips of effective communication with other health care providers:

- Begin by identifying yourself.

- Do not be judgmental
- Use professional rapport to gain respect
- Be prepared to discuss the issue at a professional level
- Propose a solution.
- Await feedback

Note that:

- You may not always have all the answers to the questions that follow.
- Be comfortable saying that you do not know the answer now, that you will investigate it and get back to the provider as soon as you can.
- The provider will respect that you provide only information about which you are confident
- Over time, you will build a working relationship with the healthcare team members that you work with.

Chapter Summary:

- Empowering clients on proper use of medicines through patient education is essential to improve treatment outcome.
- CPE will help pharmacists and other health care providers to be up to date
- Needs assessment should be a prior step to organize CPE activities
- Effective communication during medicine use education and CPEis a common tool to improve patient treatment outcomes.

Chapter Six: Poison Information Service

Chapter Description: This chapter enables the participants to discusson the magnitude of poisoning, common poisons, role of pharmacist in poison information, the common sources of poison information, and how to prepare job aids for poison management.

Chapter Objectives: By the end of this chapter, participants will be able to: provide poison information to healthcare providers, clients, the public.

Enabling Objectives: At the end of this session participant will be able to:

- Describe the magnitude of poisoning
- Identify common poisons of public health significance in Ethiopia
- Identify common sources of poison information
- Describe poison management information service
- Prepare job aids for common poisons management

Chapter Outline:

- Introduction
- Global and National Magnitude of poisoning
- Common poisons in Ethiopia
- Sources of poison information
- Poison management information service
- Job Aid for common poison management

Allocaated time:180 minutes

6.1 Introduction

Poisoning is an exposure to an amount of substance that is likely to produce unwanted effects in an individual. There are six basic modes of exposure to poisons: ingestion, ocular exposure, topical exposure, envenomation, inhalation, and trans-placental exposure. Poisonings may be the result of acute or chronic exposures and it is common to children and adults. The most important difference between pediatric and adult poisoning is by the type of agent. Higher percentage of cases in adults occur from psychopharmacologic drugs (sedatives, tranquilizers, and antidepressants). While the higher frequency of poisoning in children are caused by exposure to household, personal care products, and plants.

Poison information service (PIS) is a specialized area of medication information that pharmacists practice in providing information on poisons. This service helps to provide accurate and timely information to enhance the quality of emergency care to patients. A DI Pharmacist must be prepared to provide information on the management of any poison situation, including household products, poisonous plants and animals, medications overdose, and other chemicals. PIS can also be provided in Poison Information Centers (PIC) which are specialized units that provide expert advice on the management of poisoning or suspected poisonings to the public and health professionals.

Ethiopian Hospital Services Transformation Guidelines (EHSTG) sets that DIS shall also provide poison information services, which support adult and pediatric emergency and critical care services. This involves providing consultation to healthcare professionals in the management of poisoning, drug overdose and envenomation. In addition, FMOH has prepared guideline for poison control center and poison management hand book.

6.2 The Global and National Magnitude of poisoning

6.2.1 Global Magnitude of poisoning

The global incidence of poisoning and the severity of cases reported are unknown. It is speculated that up to half a million people die each year as a result of various kinds of poisoning, including poisoning by natural toxins. In 2012, WHO estimated 16, 500 deaths from unintentional poisoning in 16 African countries. In addition, unintentional poisoning caused the loss of 1,128,500 years of healthy life (disability adjusted life years, DALYs) in these countries. These figures underestimate the true impact of poisoning since they do not include intentional self-poisoning or poisoning due to

snakebite. It has been estimated, for example, that there are 7800 deaths per year in Africa due to deliberate ingestion of pesticides and between 1400 and 10 000 deaths from snakebite in eastern sub-Saharan Africa.

6.2.2 National Magnitude of poisoning

Activity 6.1 Brainstorming on poisoning

- Have you ever experienced a poisoned patient?
- What was the poisoning agent?

Ethiopia is widely using various chemicals in industries, and herbicides and pesticides for agriculture. Most of these chemicals contain hazardous substances and impurities that can harm human health and environment if not properly managed. It is difficult to find comprehensive epidemiology of poisoning in Ethiopia since only a few of researches were conducted. It is also very difficult to obtain accurate figures for the number of poisoning cases since cases are often poorly recorded.

For example, a study done in Gondar University teaching hospital, showed that 0.45% of all emergency admissions were due to poisoning. This study indicated that organophosphates, rat poison and alcohol were the major cases for suicidal as well as para-suicidal intentions. Another study conducted at Tikur Anbessa comprehensive specialized hospital assessed pattern of acute adult poisoning. Out of 116 adult patients presented with poisoning from January 2007 to December 2008, the number of females exceeded the number of males. The mean age was 21 years, most being (96.5%) intentional self-harm poisonings. Household cleansing agentswere the leading causes (43.1%) followed by organo-phosphates(21.6%) and phenobarbitone (10.3%) (Mekonnen and Azaji, 2011).

Concerning the distribution of acute poisoning in Ethiopia, WHO reported that acute poising accounts 0.5% of distribution causes of intentional and unintentional injuries in 2012. The weighted pool percentage of seven studies in Ethiopia showed that Organophosphate (47.2%) were the leading cause reported. The other reported causes of poisoning were sodium hypochlorite (bleaching agents) 12.9%, Drugs (10%), Herbicide (6.2%), Hydrocarbons (2.9%), Alcohol (2.9%), carbon monoxide (1.4%), and in 14.8% the cause was not identified (Esayas T. G/Mariam et al).

Moreover, Health Management Information System of FMOH for fiscal years 2001 to 2004 (July 1, 2008 to June 30, 2012) indicated that there is an increased morbidity and mortality due to poisoning with more cases falling under 9-14 years of age.

6.3 Source of Poison Information

In chapter two, primary, secondary and tertiary sources of drug information were discussed in detail. The following are some of tertiary and secondary sources specifically for poison information. Specific Primary literature can be obtained for specific poisoning cases. Details of sources of poison information are attached to the annex 2.1 of your participant manual.

Tertiary sources of poison information

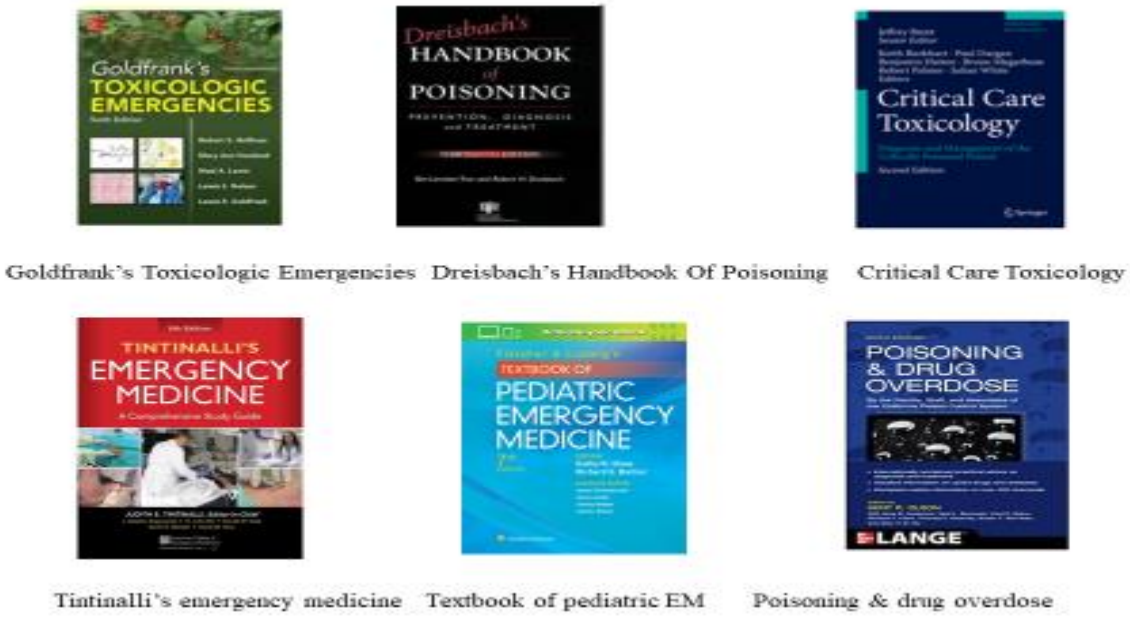


Figure 6.1; Tertiary sources of poison information

Secondary sources of information:

Monographs (Including Computer Databases)

- MICROMEDEX www.micromedexsolutions.com
- TOXINZ, http://www.toxinz.com/
- TOXBASE. http://www.toxbase.org/
- TOXNET https://www.toxnet.nlm.nih.gov
- HYPERTOX
- POISINDEX

Case study 6.1 Excercise on sources of Poision information	
Directions: Read the case below and answer the questions.	
	A 48-year-old male presents to your Emergency Department complaining of abdominal pain and intractable vomiting and diarrhea for approximately two hours duration. The patient reports that he was working in a farm earlier that morning and spilled chemicals all over his hand. He kept working and did not wash them off. Presented symptoms include weakness and "twitching" of his arms.
Physical Examination: T: 99 °F HR: 165 bpm RR: 8 breaths per minute BP: 172/95 mm Hg General: Pale and agitated male in no acute distress. HEENT: Miotic pupils. Clear drainage noted from bilateral eyes. Pulmonary: Diffuse rales and wheeze. CV: Regular rate and rhythm. Neurologic: Lower and upper extremities are symmetrically weak. Sensory exam is normal. A General Practitioner called you and informed that he has a patient with organophosphate poisoning. He urgently needs the management.	
Questions	What source of poison information you use to respond this case scenario?

Case study 6. 2: Excercise on sources of Poision information	
Directions: Read the case below and answer the questions	
	A 33-year-old male factory worker presents to the emergency department from work with complaints of muscle twitching, facial grimacing and a seizure. The company has recently acquired a new factory and he was in the process of cleaning up some white powder when he developed symptoms. A phone call to the previous owners identified the substance as rat poison, which had been

	placed to eliminate the rats in the building.
Physical Examination: T: 98.6°F HR: 80 bpm RR: 18 breaths per minute BP: 120/76 mm Hg	
General: Awake and alert.	
HEENT: Examination is normal.	
Pulmonary: Clear to auscultation.	
CV: Regular rate and rhythm without murmur.	
Abdomen: Soft and non-tender.	
Neurologic: Cranial nerves II-XII intact. Intermittent opisthotonos.	
Questions	What source of poison information you use to respond this case scenario?

6.4 Poison management information service

A drug information pharmacist provides overall information on drugs and poison. All requests for information to a poison are urgent, with an average response time of 5-minutes, compared to the general drug information service which might take 30 minutes to days to respond depending on the urgency of the call and complexity of information required.

In providing information on poison management, gathering of appropriate information related to the poisoning facilitates the identification of the potential health risk to the victim. The following information should be obtained:

1. Who was exposed? Age, Sex and weight are important.
2. What substances were involved in the exposure? As far as possible, the exact name of the product must be obtained. If this is not available, a clear description of the agent and its packaging may be useful.
3. How much of the potentially toxic agent was involved in the exposure? The number of tablets or the volume of solution that the patient is thought to have been exposed should be mentioned.
4. Time of exposure is important to determine the urgency of the situation. If exposure has just occurred and symptoms have begun action must be taken rapidly.
5. The condition of the victim at the time of call will help in determining the type and rapidity of medical response that is required.

6 Does the victim have any previous history of other medical problems? This will help to classify whether it is intentional or accidental.

7 Any initial measures already taken will need to be known and documented

A pharmacist in poison information service therefore, is required to be familiar with clinical toxicology and be able to obtain a complete history from the victims/caregiver. In addition, the pharmacist is required to know where and how to search the required information, and the ability to communicate the information properly. The approaches in management of poisoning could be general and/or specific.

The general approach in management of poisoned and overdosed patients includes:

- Resuscitation (airway, breathing and circulation),
- Risk assessment,
- Decontamination
    - Skin,ocular and gastro-intestine decontamination (gastric lavage, whole bowl irrigation, and activated charcoal)
- Specific antidote
- Enhanced illumination
    - Urine alkalization
    - Dialysis
- Psychiatric evaluation and disposition

Example: Organophosphates and Carbamates poisoning

They are widely used pesticides that may cause poisonings after accidental or suicidal exposure and are particularly common in rural areas where more potent agents are widely available.

Household insect sprays used in agricultural insecticides and home use products contain low-potency organophosphates or carbamates. Examples of organophosphates include Malathion, parathion, and tetraethyl pyrophosphate (TEPP).

I. **Mechanism of toxicity:** Organophosphate derivatives inhibit the enzyme acetyl - cholinesterase, resulting in accumulation of excessive acetylcholine at cholinergic receptors.

II. **Pharmacokinetics:** organophosphates and carbamates are well absorbed by inhalation and ingestion and through the skin. Some organophosphates may lead to delayed and persistent toxicity for several days after exposure.

III. **Toxic dose**: there is a wide spectrum of relative potency of the organophosphates and carbamates. The degree of intoxication is also affected by the rate of exposure (acute versus chronic

IV. **Clinical presentation**: four clinical syndromes are identified following organophosphate exposure; acute poisoning, intermediate syndrome, chronic toxicity, and organophosphate induced delayed neuropathy.

V. **Signs and symptoms** of acute organophosphate poisoning usually occur within 1–2 h of exposure but may be delayed up to several hours, especially after skin exposure. Clinical manifestations may be classified into peripheral muscarinic and nicotinic as well as CNS effects. Vomiting, diarrhea, abdominal cramping, bronchospasm, miosis, bradycardia, and excessive salivation and sweating. Nicotinic effects include muscle fasciculations, tremor, and weakness. Central nervous system poisoning may cause agitation, seizures, and coma. Some organophosphates may cause a delayed, often permanent peripheral neuropathy.

VI. **Chronic toxicity** is seen primarily in agricultural workers with daily exposure, manifesting as symmetrical sensorimotor axonopathy.

VII. **Diagnosis**: is based on history of exposure and the presence of characteristic peripheral and central manifestations of acetylcholine excess.

VIII. **Treatment**

1 **Emergency and supportive measures:**

- *R*escuers and health care providers must take measures to prevent direct contact with the skin or clothing of contaminated victims, because secondary contamination and serious illness may result, especially with potent pesticides and nerve agents.
- ABC of life: pay careful attention to respiratory muscle weakness; sudden respiratory arrest may occur. If intubation is required, one should be aware of potential interactions between neuromuscular blockers and cholinesterase inhibitors.
- Administer supplemental oxygen.
- Monitor patients for hydrocarbon induced pneumonitis, treat seizures, and coma if they occur.

- Observe patients for at least 6–8 h to rule out delayed-onset symptoms resulting from skin absorption.

Decontamination:

- The management of a patient who has ingested organophosphates must always include safeguards against exposure for the persons who treat the patient because the organophosphates are readily absorbed through the skin and mucous membranes. If there is heavy liquid contamination with a solvent, clothing removal and victim decontamination should be carried out outdoors or in a room with high-flow ventilation.
- Skin: remove all contaminated clothing and wash exposed areas with soap and water, including the hair and under the nails. Irrigate exposed eyes with water or saline.
- Ingestion
  - Pre-hospital: administer activated charcoal, if available. Do not induce vomiting because of the risk of abrupt onset of toxicity.
  - Hospital: administer activated charcoal (cathartics are not necessary if the patient already has diarrhea). Perform gastric lavage for large recent ingestions.

2 **Enhanced elimination:** dialysis and hemoperfusion are not generally indicated because of the large volume distribution of organophosphates and effectiveness of the specific therapy described above.

3 **Specific drugs and antidotes:** include the antimuscarinic agent atropine and the enzyme reactivator pralidoxime.

- **Atropine**
  - Atropine sulfate given in a dose of 0.05 to 0.1 mg per kg to children and 2 to 5 mg for adolescents and adults.
  - Repeated every 10 to 30 minutes till full atropinization.
  - The end point of atropinazation is clearing bronchial secretions and pulmonary rales.
  - Therapy is continued until all absorbed organophosphate has been metabolized and may require 2 mg to more than 2,000 mg of atropine.
- **Note**: Atropine will reverse muscarinic but not nicotinic effects.
  - After atropinization has been instituted, severe poisonings should be treated with the addition of pralidoxime.
  - It acts to regenerate the enzyme activity at all affected sites, however, it does not reactivate plasma cholinesterase.

- A dose of 25 to 50 mg per kg should be administered in 100 mL of saline by infusion over approximately 30 minutes; adults may receive 1 to 2 g by IV.
- The end point should be persistent relief of neurologic and cholinergic signs.
- Pralidoxime is not generally recommended for carbamate intoxication, because in such cases the cholinesterase inhibition is spontaneously reversible and short-lived.

Note:
✓ Organophosphates are usually dissolved in hydrocarbon bases. Thus, the clinician should be prepared to treat hydrocarbon induced pneumonitis if it develops. Also, bronchopneumonia that complicates pulmonary edema has been observed in acute poisonings. Because organophosphates cause elevated levels of acetylcholine in the plasma, compounds that affect the uptake of acetylcholine and/or its release should be avoided in the management of these patients. Specifically, aminophylline, succinylcholine and phenothiazines are contraindicated.
✓ Death from organophosphate poisoning usually occurs in 24 hours in untreated patients, usually from respiratory failure secondary to paralysis of respiratory muscles, neurologic depression, or bronchorrhea.

Role of DI pharmacist in Poison Information

Activity 6.2 Drill on role of DI pharmacist in poison information

- Have you ever encountered any query related to poisoning?
- Where did the query come from (from facility or community)?
- How did you manage the query?

The pharmacist working in DIS is expected to provide information and advice concerning the toxicity of chemicals, the risk they pose, their prevention and treatment. The information can be given to healthcare professionals, the media, the public, and other concerned. Some of the roles of pharmacist in the provision of poison information are mentioned below

- Provide comprehensive and evidence-based information to health professionals about management of poisoning, envenomation and drug overdose.
- Educate clients and the general public through different medias (mass education, printed materials, mass media, website, telephone …).
- Develop, implement, and evaluate measures for toxicovigilance activities.
- Support management of poisoning cases at the scene, pre-hospital and in facilities

- Prepare educational material on the prevention of poisoning for both health care professionals and the public, including material for use in emergency, inpatient and outpatient.
- Undertake toxicovigilance activities
- Participate in in-service and pre-service trainings to healthcare professionals

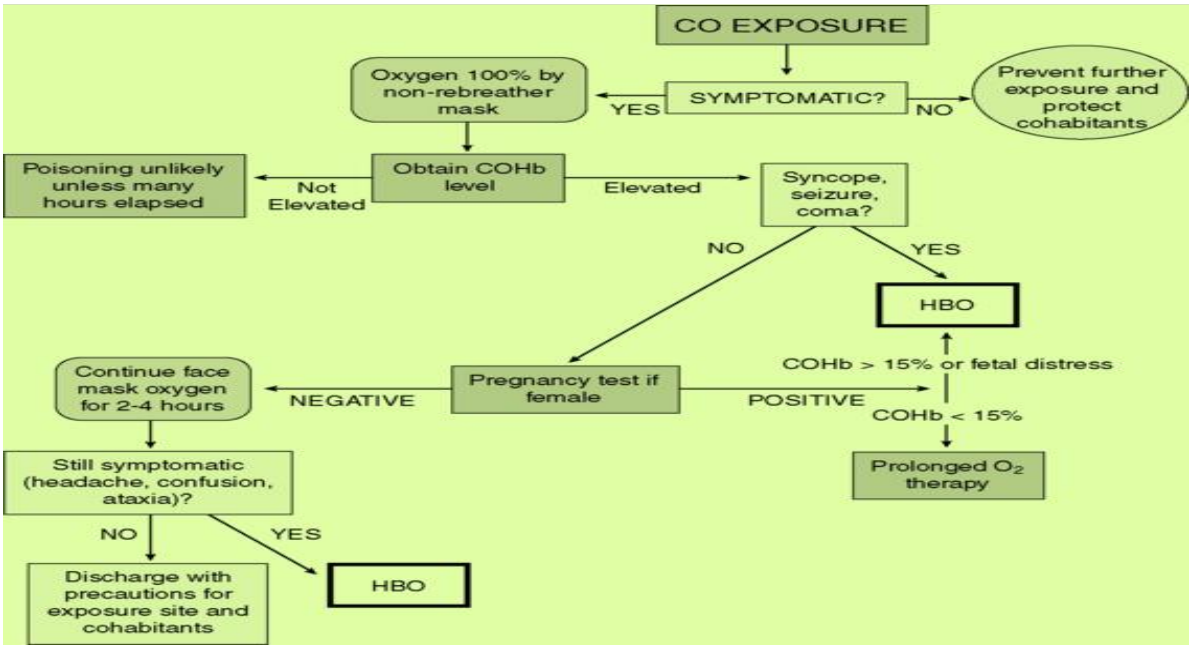
6.5 Job Aid Preparation for common poison Management

Job aids are tools (such as instruction cards, memory joggers, wall charts) that allows an individual to quickly access the information needed to perform a task. A pharmacist working in DIC needs to proactively prepare different job aids and disseminate to emergency and critical care units. Job aids provide just the right amount of task guidance and support, at the moment of need, as part of work. The job aid can be prepared for general management as well as specific to a certain poisoning agent. Presented below is the tips for preparation in management of poisoning. Illustrated sample job aids in the management of carbon monoxide poisoning and snake bite will follow.

Table 6.1. Tips for preparing Job Aids

Content	• Include only the necessary steps or information required. Ask yourself if the step or content is relevant to the task at hand. • Keep the information simple and concise. Present the information in small pieces. • Write short sentences and use short words to describe or list the steps, processes, calculations, or decisions that need to be made • Leave out "nice-to-know" information. The job aid should be a quick reference. • Place critical information in the first and last parts of sentences or sections of the job aid.
Language	• Use common, everyday language. Avoid long, unfamiliar words and jargon unless appropriate to the task and employee. • Use verbs and actions words at the beginning of sentences wherever possible.
Visual Elements	• Use clear and simple drawings, graphics, diagrams and pictures to clarify information or provide more detail than words would allow. • Be consistent in the type of visual that is used. If you use a drawing in one step, use one in any subsequent steps.

Below illustrated is the treatment algorithm for Carbon monoxide poisoning.



HBO: Hyperbaric Oxygen

Figure 6.2 A treatment algorithm for carbon monoxide poisoning

Job Aid: Snake bite treatment using Antivenom

- For patients with documented envenomation, be prepared to administer specific antivenin.
- Give **monovalent antivenom** if the **species of snake is known**.
- Give **polyvalent antivenom** if the **species is not known**.
- Follow the dose and directions given on the antivenom preparation.
- The dose for children is the same as for adults.
- Dilute the antivenom in 2–3 volumes of 0.9% saline and give intravenously over 1 hour.
- Check for any reaction Before antivenom administration (test dose of 0.02-0.03 ml of 1:10 diluted antivenom in normal saline must be given intradermally)
- Give more at a dose of 5 ml/min or diluted in Isotonic fluid and infused over 30-60 min initially and monitor closely for anaphylaxis or other serious adverse reactions.
- Give more anti-venom after 6 h if there is recurrence of blood clotting disorder or after 1–2 h if the patient is continuing to bleed fast or has deteriorating neurotoxic or cardiovascular signs.
- Life-threatening anaphylactic reactions (skin rash, itching, fainting, shortness of breathing etc) may occur with antivenin administration, even after a negative skin test. Prepare IM epinephrine (adrenaline) 10 µg/kg (0.1ml/kg of 1 in 10,000) IM and IV chlorpheniramine (if available) and be ready if allergic reaction occurs. Promethazine IM or IV can be given if allergic reaction occurs in antivenom administration.

Activity 6.3 Exercise on preparing jobAid	
Directions: Read the case below and answer the question.	
	In 2016, more than ten adult patients have been admitted to Tikur Anbessaspecialized hospital with phenobarbitone poisoning. Currently it is becoming a common problem. You are working as a DI Pharmacist at Tikur Anbessaspecialized hospital.
Question/Instruction: Prepare Phenobarbitone management job aid to be posted at the emergency unit of the hospital	

Chapter Summary

- The most common type of poisoning in Ethiopia are organophosphates, house hold chemicals and detergents, alcohol and drugs.
- The pharmacist working in DIS is expected to provide information and advice concerning the toxicity of chemicals, the risk they pose, their prevention and treatmentThe management of poisoning involves general and specific approaches
- Pharmacist must know different sources of poison information
- The drug information pharmacist is expected to prepare different job aids in the management of poisoning

Chapter Seven: Role of Drug Information Service in Pharmacy Service Activities

Chapter Description: This chapter enables the participants to discuss the role of Drug Information Service in pharmacy service activities.

Chapter Objective: By the end of this chapter, participants will be able to:explainthe role and support on the pharmacy services activities.

Enabling Objectives: By the end of this chapter, participants will be able to explain the role of DIS in: -

- Pharmacovigilance
- Drug and Therapeutics Committee
- Clinical Pharmacy
- Drug Supply Management

Chapter Outline:

This chapter has the following outlines:

Role of Drug Information Service in:

- Pharmacovigilance (Adverse Drug Event Monitoring and Adverse Drug Event Reporting)
- Drug and Therapeutics Committee,
- Clinical Pharmacy service

Allocated Time:145minutes

7.1 The role of Drug Information Service in pharmacovigilance

Introduction

Medicine safety problems are commonly caused by medication errors, poor quality, and certain medicines that are inherently unsafe (cytotoxic drugs, for example). Such safety problems are manifested through adverse drug events, which may result in serious patient harm and/or death, extended hospital stay and large consumption of resources.

Adverse Drug Events (ADE) is defined as any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.

ADE encompasses harms that occur during medical care that are directly caused by the drug. These harms can include, but are not limited to, medication errors, adverse drug reactions, allergic reactions, and quality defects.

- **Medication Errors:** is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer
- **Adversedrugreaction(ADR):** isharm directly causedby themedicine at normaldoses, duringnormal use.
- **SideEffect**: Effects that may bewell-knownandevenexpectedandmay requirelittleornochangeinpatient management.
- **Product quality defect:** Quality problems of products i.e; suspected contamination, questionable stability, defective components, poor packaging or labeling, or unexpected therapeutic ineffectiveness

In the last decade morbidity and mortality due to medicines is one of the major health problems. It has been estimated that ADR is the 4th to 6th largest cause for mortality in the USA. They result in the death of several thousands of patients each year, and many more suffer from ADE. The percentage of hospital admissions due to adverse drug reactions in some countries is about or more

than 10%: Norway 11.5%; France 13.0% and UK 16.0%. In addition, services to treat ADE impose a high financial burden on health care due to the hospital care of patients with drug related problems. Some countries spend up to 15-20% of their hospital budget dealing with drug complications.

There is very limited information available on ADE in developing countries and countries in transition. However, one may expect that the situation is worse rather than better. The problem is also aggravated by lack of regulations related to pharmacovigilance including ADE reporting, circulation of substandard and counterfeit products, irrational use of drugs and lack of independent information. Hence, a close monitoring and evaluation of most medicines is necessary to prevent more serious damage from occurring.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Hence, Pharmacovigilance system is needed for the prevention of drug-induced human sufferings that arise because of the occurrence of adverse drug events. The ultimate goals of pharmacovigilance are:rational and safe use of medicines**,** assessment and communication of the risks and benefits of drugs on the market and theeducating and informing of patients. In health facility settings, the DIS Pharmacist plays a vital role in medication safety monitoring.

Pharmacovigilance at health facilities

In order to prevent patients suffering from injuries by adverse events and get a better treatment outcome, facilities should be the vanguard force in the monitoring of drug safety. The best way to implement this would be using DTCs which should make assessing and managing drug safety as one of its core functions.DTCs should implement programs that track ADEs, report to the national center and use the information for the improvement of health care. Hence, the DTC should assign a focal person who will follow these activities. The DI pharmacist would be the appropriate person to work with the focal person or serve as focal person who assists the health facility's DTC, to monitor adverse drug events.

Activity 7.1 Think -pair and share the role of DIS

	What roles does the DIS should play in the pharmacovigilance activities?

The Drug Information Pharmacists can be deployed to:

- Assist in monitoring the safe and effective use of available medicine, which certainly includes the management of ADE.
- Play an essential role in developing communication materials like newsletters and other publications, which are utilized by different professionals for disseminating drug alerts and other drug safety information.
- Provide support to dispensing pharmacists to improve patient safety and quality of life during the counselling session.
- Analyze ADR reports to include statistical analysis of prevalence, severity, and trends in the occurrence of ADRs at their facility
- Organize discussion and evaluation of reports by the DTC on a regular schedule and communicate the information to the clinical staff
- Recommend corrective managerial (amend formulary or Standard Treatment Guidelines to include a drug of proven safety based on the information obtained from the analysis), educational and administrative measures and follow up on the results for further improvement of health care.
- Report to the national regulatory authority and manufacturers all observed reactions.
- Document and review medication errors and product quality problems.
- Educate and warn patients to reduce the possibility of ADR recurrence.
- Keep track of important files and documents related to patient safety to maximize the benefit and minimize the risk of medication use.
- Update his/her knowledge regarding newer drug inventions, regimens and surgical procedures.

Reporting of Adverse Drug Events

Reporting adverse drug events occurring in the health facilities helps to improve quality of patient care and health outcome. Reporting ADE is one of the core functions of DTC. The Drug Information Pharmacist is responsible in facilitating the reporting of ADE and hence:

1. Orient the staff on the definition, importance, recognition and flow of reporting of ADEs.
2. Avail and orient health care providers on how to fill the ADE Reporting Form.
3. Avail adequate copies of the prepaid ADE Reporting Form and distribute to all relevant service units (both outpatient and inpatient) through appropriate means.
4. Collect ADE reports from all service units, compile the reports and present to the DTC every two months.
5. Document copies of the DTC-approved reports and send the original to FMHACA.

Adverse Drug Events reporting procedures: The following SOP describes the procedures and activities when reporting ADE.

SOP for completing Adverse Drug Event formats

What to report	All suspected reaction to the drug: Unexpected reactions, unknown or serious adverse drug reactions, unexpected therapeutic effects, all suspected drug interactions, product quality problems, treatment failure, medication error.
When to perform	As soon as Adverse Drug Events are identified.
How to report	Using Adverse drug event reporting form, (annexed) and send to FMHACA via post office or email.

Steps	Activity	Note
1	**Patient background information**- write the patient background information starting from Patient name; Card No., Age, Sex, Weight, Height, Ethnic group and Substance abuse.	It's not necessary to write the full name of patient's, write initials only. Substance abuse: refers to the harmful or hazardous use of psychoactive substances, including alcohol, chat, cigarettes and illicit drugs.

2	**Drugname**: write all information includingbrand name and manufacturer	Avoid Non – Standard Abbreviations
3	**S/C**: Fill all Suspected and concomitantlyused drugs	Write 'S' for suspected drugs and 'C' for concomitantly used drugs
4	**Product Dosage and Frequency**: write dose/ dosage form, route and frequency of the drug	Use appropriate abbreviations for frequencies, when necessary. Take care in writing units (e.g. mg, mcg, etc).
5	**Date**: write the start date, the date the reaction started and date the drug was discontinued.	In European calendar (dd/mm/yy). If the medicine hasn't been discontinued at the time of reporting, write'continuing'
6	**Indication**: write the reason for use of the	
7	**AdverseDrugEventDescription**	Clear description about the nature of adverse event, the date of onset, duration, time course and laboratorytest results including '-ve' and normal results of any relevant test performed should be reported. The severity of the reaction i.e whether it has necessitated prolonged hospitalization or not, discontinuation of the medicine or not, etc has to be reported.
8	**Reaction necessitated**: Discontinuation of drugs: tick yes or no Hospitalization: tick yes or no	
9	**Reactionsubsides** after discontinuation of suspected drug: tick yes or no	
10 11	**TreatmentReaction**: write any treatment given at the facility for the identified ADE (Reaction).	
12	**Outcome**: tick the outcome of the ADE	Example: died, not recovered with or with out
13	**Sequelae**: write any sequelae condition that result due to the ADEs	Sequelae: is a pathological condition resulting from a prior disease, injury or attack.
14	**Relevantmedicalconditions**: write any relevant medical conditions if occurred	Examples: Allergies, renal disease etc

15	**Reportedby**: write the name, the profession, email address, telephone, name of the individual reporting the ADE and their institution and date of reporting	
16	**ProductQualityproblem** write drug trade name, batch no, dosage form, strength, the size/type of package of the suspected drug	Example: color change, separating of components, powdering, molding etc
17	**Forofficeuse**: leave empty	This section of the form is to be used by the regulatory body to which the ADE is reported
	From: write your postal address at the end of postage	Put the postal address (B. O. Box) of the health facility
18	Provide the completed format to the ADE focal person	

The ADEs report is completed when:

1. ADE focal person or DIS pharmacist sends the completed ADE reporting format to FMHACA and summary report to the facility DTC.
2. When the focal person routinely follows and communicates to the responsible body.
3. When the focal person receive confirmation from the nearest FMHACA or regional regulatory bodies.
4. When the DTC takes measures on the reported ADE until FMHACA takes the appropriate measures and gives feedback and the feedback is implemented.

Case Study 7.1 for ADE reporting	
	1. Ato NT is 48 years old known hypertensive patient (card number 23076) went for a follow up to **AB** hospital found in Addis Ababa, woreda 09 kebele 14 on 14/6/2008E.C. While the healthcare provider (S/r Zewde) was measuring his BP it is found 185/120 mmHg. He smokes half a pack of Nyala Cigarettes a day. 2. Ato NT was admitted to emergency room for 12 hours and prescribed ABC brand of Hydralazine 20mg/ml injection to be given 5mg every 20minutes until BP drops and XYZ® brand of Furosemide 10mg/ml in 2ml injection; 20mg dose daily for three days. The nurse gives the two medications as

	prescribed. 3. Ato NT gets improvement and discharged after 12 hours of stay in emergency room. On the next day, AtoNahom comes to the hospital with complains of red, swollen skin on his legs and becomes very sick and was admitted to medical ward in AB Hospital. Hydralazine 20 mg/ml injection was produced by Parma lab firm **Q** with batch number of ABA612CXF and expiry date of 29/2/2020 and XYZ® which produced by pharma firm **Z** with batch number of AA1012AXA and expiry date of 31/7/2020. Next morning when the duty healthcare provider was about to give Furosemide she found out it was cloudy. The nurse decided to stop the Furosemide medication temporarily and the swelling subsides after five days and he became stable of discontinuation of medication.
Assume you were the pharmacist in-charge of the DIS whom the healthcare provider reported the case to you. Question: 1. How would you report Ato NT`s case? 2. Follow the SOP to fill the case and submit for review.	

7.2 Role of Drug Information Service in Drug and Therapeutics Committee

The health facility's DTC supports and oversees establishment and functioning of Drug Information Services. The DIS is the center of resource for the DTC in formulary preparation and revision, conduct medicine use studies and design intervention strategies. Hence, DIS works with DTC to:

- Organize continuing education for health professionals
- Participate in drug use evaluations
- Assist in the development of investigational drug studies and participate in maintenance of appropriate records and reports
- Support the review of formulary system by preparing drug monographs and conducting drug utilization reviews
- Participate in the Anti-Microbial Resistance prevention and containment

Evaluating and Selecting Medicines for the Formulary

Appropriate selection of medicines can achieve the results of cost containment and enhanced equity in access to essential medicines and improve quality of care. They are selected with due regard to many factors, such as disease prevalence pattern; treatment facilities; the training and experience of available personnel; financial resources and evidence of efficacy, safety, quality, and comparative cost-effectiveness. Selecting medicines for the list is the most important function of the formulary system. Hence, the DIS will play a significant role in supporting DTC in selecting medicines for the health care system. The following represent major supports that the DIS could contribute in the management of the formulary system:

- Compiling information resources
- Performing evaluation using established criteria
- Obtaining expert opinion and recommendations
- Writing medicine monograph describing the evaluation and results
- Developing drug list recommendations and present to the DTC meeting
- Making informed decisions at the DTC meeting
- Disseminating the result of the evaluation, recommendations, and DTC's decision

Adequate resources to obtain information and to evaluate the efficacy, safety, quality, and cost of a medicine are essential. Unbiased sources of information are required in accurately evaluating medicines' characteristics. A comprehensive review of journal articles, especially of randomized controlled trials and meta-analysis could provide unbiased information. The DI pharmacist is responsible for providing evidence-based information during the development of the health facility specific medicine list; additions or deletion of medicines following specific policies and procedures developed for the DTC. The DI pharmacist must prepare and submit recommendations for DTC decisions on each medicine addition and deletion requests. A transparent methodology must be deployed, and monograph prepared for these important decisions.

Case Study 7.2 writing a monograph for formulary management decision	
	A request from the physician working in Internal Medicine submits deletion of Amitriptyline from the hospital's medicine list based on the monograph of Imipramine that the DI pharmacist submitted as per the physician's request (refer the monograph section at 4.2 of your participant manual). Furthermore, the side effect profiles of the two drugs are the main reason for his request that

	more patients complained of side effects on Amitriptyline than on Imipramine. Hence you are requested to submit your recommendations.
Question: Write a monograph on amitriptyline, compare with impiramine and submit your recommendations for the DTC's decision.	

Drug Use Studies

DIS is best suited to undertake and coordinate drug utilization studies in the facility. The studies should focus on priority problem areas of the facility and be action-oriented. Such studies should be repeated at specified intervals to measure the effectiveness of interventions implemented. In undertaking drug use studies, the DI Pharmacists in collaboration with other DTC members and the staff should:

1. Identify areas to be investigated based on available information
2. Develop research proposal and get approval from the health facility DTC
3. Conduct the study
4. Write report and submit it to the DTC
5. Present the findings and recommendations to staff of the health facility
6. Follow on implementation of recommendations
7. Repeat the study after a certain period of time
8. Facilitating dissemination of findings through organization of sessions, publication (bulletins, abstracts and journals) and follow the implantation of recommendations

AMR containment and prevention

The use of antimicrobial medicines has greatly contributed to the decline in morbidity and mortality by infectious diseases over the past half-century. This achievement, however, is being undermined by the rapidly growing problem of antimicrobial resistance (AMR). Irrational use of antibiotics has greatly favored the emergence and spread of resistant microorganisms.

DIS can collaborate with other health facility units and committees resulting in synergistic action to contain the threat of AMR with the following:

- **Differentdepartments**: for education of medical students, physicians, pharmacists, nurses, and patients
- The **InfectionControlCommittee**: for the o reduction of the spread of resistant pathogens

- The **microbiologydepartment**: for collection and management of information on pathogens and resistant patterns
- **Healthfacilitymanagement**: for developing and implementing policies on antibiotic use
- **Antimicrobialstewardshipprogram**: Support in the development of Terms of Reference, Plan of action, antimicrobial use guideline, training etc.
- **Pharmacy**: To improve antimicrobial procurement and quality.

7.3 Role of Drug Information Service in Clinical Pharmacy practices

The pharmacy professional needed today is a knowledgeable drug expert and skilled, persuasive communicator and not a pill counter. This pharmacist embraces a new practice model of pharmacy care.

The DIS in the health facility is expected to strengthen the Clinical Pharmacy Service by:

- Creating awareness for the staff and management,
- Fulfilling reference materials for clinical-oriented pharmacists,
- Responding to drug information queries and perform follow-up
- Dissemination of relevant information to the clinical staffs.
- Performing search for questions forward by the clinical staff.
- Assist in organizing morning sessions and pharmacy seminars
- Facilitate in-service trainings and experience sharing events with best performing hospitals on clinical pharmacy services and other related activities which can strengthen the service

In summary, DI Pharmacists may or may not participate directly in the decision-making process of patient care but perform a valuable supportive role which culminates in improved patient care.

Nevertheless, each pharmacist working on the provision of drug information must set aims and objectives for the service in terms of: what is to be achieved by providing such a service, and, the role of the pharmacist in optimizing patient care.

7.4. Role of DIS in Drug Supply Management

Pharmaceuticals supply management encompasses the planning and management of all activities involved in selection, quantification, procurement, storage, distribution and delivering a final product or service, fromthe initial supplier to the end-user.

Supply management should integrate supply and demand management within and across the health facilities. Pharmaceuticals need to be managed properly starting from product selection until used rationally. Therefore, the major reasons to manage medicines properly include:

- Pharmaceuticals are part of the link between the patient and health services. Consequently, their availability or absence will have a positive or negative impact on health.
- The issue of medicines is not the responsibility of health workers only. It has political,economic, and social dimensions.
- Poor medicines management obstructs access to medicines results in wastage and health hazard.
- Access to medicines is a fundamental human right.

Activity 7.2 Drill on role of DIS in DSM	
	What roles could DIS play in the Drug Supply Management?

DIS will help DTC in inventory management, storage and distribution of medicines within health facility which include:

- Avail the necessary information or assist Review medicines list of each dispensing units.
- Disseminate stock status updates by providing updated information to the health care providers and management on overstock, near expiry, new arrival etc.

To summarize DIS has play a vital role to improve medicines supply system and reduce cost and wastage.

Chapter Summary:

- ADE does constitute a serious problem, increasing morbidity and mortality and health care costs worldwide. (Y/N)
- What adverse drug events should be reported?
- When should ADE be reported?
- The DI Pharmacist provides a variety of support services in the healthcare facility. Mention DIS supports to:
    - DTC
    - Formulary system
    - Clinical pharmacy
    - Drug supply management.

Chapter Eight: Ethical and legal issues of Drug Information Service

Chapter Description: This chapter enables the participants to introduce the legal and ethicalprinciples that are specific to drug information and discuss the application of ethics and law while providing drug information service.

Chapter Objective: By the end of this chapter, participants will be able to: follow ethical and legal principles in practicing DIS.

Enabling Objectives: At the end of this chapter participants will be able to:

- Discuss the basic ethical and legal principles
- Explain specific ethical and legal issues related to DIS activities
- Apply ethical and legal principles while providing DIS

Chapter Outline:

This chapter has the following outlines:

- Basic ethical and legal principles applicable to DIS
- Specific legal and ethical issues related to DIS
- Application of ethical and legal principles while providing DIS

Allocated Time: 140 minutes

8.1 Introduction

Definitions

- **Ethics** is a set of moral principles and a code for behavior that govern an individual's actions with other individuals and within society.
- **Laws** are societal rules or regulations that are obligatory to observe. It is a set of principles enforced by the government and governed practice of healthcare professionals.

Ethiopiahas codes of ethics as well as laws. These codes of ethics and the law impose duties to be observed by professionals. Failure to maintain ethics of the profession and the law may call for legal consequences.

Like any other pharmacy practices, the ethical and legal principles applied for pharmacists are applicable to DI pharmacist.

8.2 Basic Ethical and Legal Principles Applicable to Pharmacy profession

There are general and specific ethical and legal principles applicable to pharmacy profession in which is also applicable to DIS. Some of the general principles governing pharmacists are listed as follows:

a. ***Non-maleficence:***"*Do no Harm*". Non-maleficence is the obligation to avoid or not inflict harm on others whether intentionally or unintentionally. Non-maleficence expresses the limits of the principle of beneficence (discussed more thoroughly below) and reminds the pharmacist to consider the possible harms that may arise with any intervention. The presence of harm should be avoided or prevented, however this principle also guides the pharmacist to evaluate the levels and types of harms present. For example, if a pharmacist encounters a patient who is taking a harmful medication, the action that is guided by non-maleficence is to stop the patient from taking the medication.

b. ***Beneficence:"****Duty to promote good"*. The principle of beneficence emphasizes the importance of weighing risks and benefits.

c. ***Respect the patients-professional relationship***. A moral rule often referring to respect for the health professional – patient relationship.

d. ***Justice:****"fairness"*. The principle of justice is concerned with the fair distribution of benefits and burdens.Concerns of justice often arise when resources are scarce, or inequality is present.

While there are various models of fair distribution to provide patients with resources or opportunities, the goal of these models is ultimately to protect vulnerable members of society and to minimize undue burdens, including the lack of available and accessible resources.

e. ***Consent:*** *"right to be informed"*. A moral rule related to the principle of autonomy which states that the client has the right to be informed and freely choose a course of action. E.g., informed consent to receive a therapy or a procedure.

f. ***Confidentiality:*** *"right to give or refuse consent"*. A moral rule also related to a principle of autonomy, which specifically addresses client's right to give or refuse consent relative to release of privileged information.

g. ***Privacy:*** *"right to control own affairs"*. The right of the individual to control his or her own affairs without interference from or knowledge of outside parties.

h. ***Veracity:*** *"truth telling or honesty"*. Related to the principle of autonomy is the principle of veracity, or truthfulness. When informing and educating patients and caregivers, it is critical to provide truthful information even though such information may involve "bad news" or be perceived as harmful to the overall well-being of the patient. It is important to establish a therapeutic relationship with patients to understand how information should be delivered as each patient may have different expectations.

In addition, there are twelve principles of ethics for general public service.These general principles for public service are directly applicable to the pharmaceutical service provision. They are the backbones of code of ethics. Please see annex-8. 1 to know the twelve principles.

8.1.1 Code of Ethics for Pharmacists Practicing in Ethiopia

There is code of Ethics for Pharmacists Practicing in Ethiopia that was prepared and issued by Ethiopian Pharmaceutical Association (EPA) first in 1996 and the second edition in 2006. This Code, prepared and supported by pharmacists, is intended to state publicly the principles that form the fundamental basis of the roles and responsibilities of pharmacists. These principles, based on moral obligations and virtues, are established to guide pharmacists in relationships with patients, health professionals, and society. These ethical principles are outlined below;

I. A pharmacist respects the covenant relationship between the patient and pharmacist.

Considering the patient-pharmacist relationship as a covenant means that a pharmacist has moral obligations in response to the gift of trust received from society. In return for this gift, a pharmacist promises to help individuals achieve optimum benefit from their medications, to be committed to their welfare, and to maintain their trust.

II. A pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner.

A pharmacist places concern for the well-being of the patient at the center of professional practice. In doing so, a pharmacist considers needs stated by the patient as well as those defined by health science. A pharmacist is dedicated to protecting the dignity of the patient. With a caring attitude and a compassionate spirit, a pharmacist focuses on serving the patient in a private and confidential manner.

III. A pharmacist respects the autonomy and dignity of each patient.

A pharmacist promotes the right of self-determination and recognizes individual self-worth by encouraging patients to participate in decisions about their health. A pharmacist communicates with patients in terms that are understandable. In all cases, a pharmacist respects personal and cultural differences among patients.

IV. A pharmacist acts with honesty and integrity in professional relationships.

A pharmacist has a duty to tell the truth and to act with conviction of conscience. A pharmacist avoids discriminatory practices, behavior or work conditions that impair professional judgment, and actions that compromise dedication to the best interests of patients.

V. A pharmacist maintains professional competence.

A pharmacist has a duty to maintain knowledge and abilities as new medications, devices, and technologies become available and as health information advances.

VI. A pharmacist respects the values and abilities of colleagues and other health professionals.

When appropriate, a pharmacist asks for the consultation of colleagues or other health professionals or refers the patient.

A pharmacist acknowledges that colleagues and other health professionals may differ in the beliefs and values they apply to the care of the patient.

VII. A pharmacist serves individual, community, and societal needs.

The primary obligation of a pharmacist is to individual patients. However, the obligations of a pharmacist may at times extend beyond the individual to the community and society. In these situations, the pharmacist recognizes the responsibilities that accompany these obligations and acts accordingly.

VIII. A pharmacist seeks justice in the distribution of health resources.

When health resources are allocated, a pharmacist is fair and equitable, balancing the needs of patients and society.

Activity 8.1 Pair exercise on Ethical principles

Code of Ethics for Pharmacists Practicing in Ethiopia	**General principles governing pharmacists**	**Twelve Principles of Ethics for General Public Service**
A pharmacist:		
• Respects the covenant relationship between the patient and pharmacist		
• Promotes the good of every patient in a caring, compassionate, and confidential manner		
• Respects the autonomy and dignity of each patient		
• Acts with honesty and integrity in professional relationships		
• Maintains professional competence		
• Respects the values and abilities of colleagues and other health professionals		
• Serves individual, community, and societal needs		
• Seeks justice in the distribution of health resources		

Question/Instruction: Link the basic principles and the Twelve Principles of Ethics for Public Service against the code of ethics. Write your response on respective columns

Legal Principles Applicable to Pharmacy Practice

Laws are essential for pharmacy practice for:

- Restrictions on the use of medicine/chemicals
- Restriction on individual practice of pharmacy

The purpose of pharmacy law is to protect the public. There are relevant criminal and civil code that govern the pharmacy professionals like any other health professionals. These are:

  - Criminal code of Eth. Proc. No 414/2004
  - Civil code of Eth. Proc. No.165/1960

There are also directives the FMHACA shall issue to the implementation for health professionals. In addition, Ethiopian Council of Minsters established Ethiopian health professional council establishment Reg.No. 76/2002**.**

- Art.16. endowed with the power and duties to the professional ethics subcommittee.

8.3. Specific legal and ethical issues related to DIS

All pharmacy professionals are expected to abide with above mentioned ethical and legal principles throughout their Pharmacy practice. Provision of drug information requires accuracy and completeness of information, the expertise and judgment of the DI pharmacist based on these ethical and legal principles is critically essential. Hence, the DI pharmacist will be held liable for his/her conduct relating to drug Information. Furthermore, The DI pharmacist shall be involved in ethical decision making at all levels of provision of s drug information services.In this regard the following shall be noted:

Information resources

Information resources shall be current and appropriate to the level of service provision and shall be documented whenever used in formulating responses.

Staff

Staff shall be appropriately trained and supervised. Every effort shall be made to ensure maintenance of current awareness of the specialty.

Query taking

- Prior to answering queries, the identity of the enquirer and the reasons for the enquiry must be established.
- Patient enquires shall be referred to their local pharmacist or clinician if deemed appropriate.
- Drug information from the media or legal representatives shall be channeled through the health directorate.
- If a query is deemed unethical or illegal, the drug information pharmacist shall:
  - Refuse to answer the query or
  - Seek advice from the office of the Health Administrator, or the Solicitor on Council. However, all such queries shall be duly documented.

Note: *Queries may be deemed unethical or illegal or both when the identity of the caller and reasons for the enquiry cannot be established*.

Answering queries

- DI pharmacists shall bear full responsibility for the quality of information or advice they provide.
- When necessary; queries shall be referred to appropriate specialist for expert opinion.
- Data extrapolated from animal and in-vitro studies must be stated clearly in the response as to the origins and limitations of the information**.**
- Data from abstract of an article must be stated clearly in the response as to the origins and limitations of the information**.**
- DI pharmacist shall have responsibility to their enquirers and their welfare. However, every effort must be made to ensure that the relationship between patients and prescribers is not compromised.
- Responses shall be supported with reference and be made readily available on request.
- Responses based on interpretation or evaluation of limited available data rather than substantial information must state so.
- Information on 'non-approved' use of drugs shall be accompanied with a clear awareness of the prescriber's responsibility in prescribing outside the approved indication.

Documentations

- DI pharmacists shall ensure documentation of all queries handled.
- All documentations on drug information queries shall be kept for a minimum of 5 years.

Confidentiality

- Enquirer's identity shall remain confidential.
- Patient information shall remain confidential.
- The substance of enquiries shall always remain confidential.
- Confidential industrial information shall be kept as such.

Negligence

Currently, most litigation concerning pharmacists involves negligence. Therefore, it is safe to assume that a legal cause of action pertaining to the provision of DI will be founded on the theory of negligence as the direct or proximate cause of personal injury or death. Malpractice liability based on negligence refers to failure to exercise the degree of care that a prudent (reasonable) person would exercise under the same circumstances. Elements of negligence include the four Ds: (1) duty breached, (2) damages, (3) direct causation, and (4) defenses absent.

Information on unregistered drugs or 'off-label' use

In some circumstances medicines are used for indications, in dosages, or administered via routes of administration, other than those approved by the regulatory authority. In providing this information to an enquirer it is the pharmacist's responsibility to inform the enquirer that this is not an approved use of the drug in Ethiopia. The enquirer should be reminded of his/her responsibilities if they choose to prescribe the medicine for a non-approved indication, including the need to obtain informed consent from the patient.

Medicines information for legal purposes

Requests for information, or interpretation of data for legal purposes, should be handled with due care. Interested parties requesting such information include the prosecutor, police or health professional governance organizations. In providing response in these circumstances, the DI pharmacist is functioning as an 'expert witness' and may be required to provide evidence at any resulting court hearing. In handling requests for information concerning a patient's therapy the patient's confidentiality must be respected. If the information is required to support an expert witness it may be preferable to provide the information directly to them. Care should be taken to avoid any conflict of interest.

Bulletins and publications

Local procedures should be in place for the research, compilation, production and checking of such publications. The process should aim to minimize any risk of error and include documentation that such a procedure has been followed. If an error occurs in a publication originating from an DIS the concept of negligence may apply (i.e. if a patient suffers injury as a result of an error the author may be held legally responsible), whether or not a disclaimer has been used in the publication. Measures should be taken to withdraw the publication, correct the error and minimize the risk associated with the error as soon as it becomes apparent.

Use of Social Media

If the DIS wishes to publish information using social media (such as Facebook, Twitter, Instagram or YouTube etc.), all legal and ethical principles and codes of conduct relating to pharmacy must be upheld. Patient and institution confidentiality must also be adhered to. Any material that is posted on social media should be publicly available and within the pharmacist's range of expertise. The service should be very cautious about or refrain from taking medicines information queries via social media due to the limitations in gathering all required data and risk of third party enquiries.

Copyright law

Copyright law covers a broad range of material with the purpose of protecting the creator's creativity or intellectual effort. It enables the creator to exercise some control over possible exploitation of material they have created. Copyright law seeks to protect the creator's need to be rewarded or recognized when their work is reproduced while still enabling access to the material by potential users.

Steps to Protect Against Malpractice

As it has seen in ethical and legal issues, pharmacists will be liable if not doing their activities properly. To protect themselves, professionals shall perform his/her own activity to protect against the malpractice. The follows are steps to protect against the malpractice.

- Use adequate documentation (references)
- Keep up to date with DI and medical practice (use most up-to-date resources)
- Utilize Quality Assurance Programs
- Use disclaimers for wrong information or data published by others.

8.4 Application of ethical and legal principles while providing DIS

Ethical Dilemma

This section addresses the application of a proposed process of ethical analysis when identifying, analyzing, and resolving ethical dilemmas that may arise during pharmacists' provision of drug information. Ethical dilemmas are common during DI, particularly with regard to patient confidentiality, enquiries from patients and those that potentially impact on the relationship between the patient and other health professionals responsible for their care. It is important to adhere to the basic ethical principles outlined above. Time should be taken to consider any ethical issues. If necessary, advice from more experienced colleagues, managers or legal input should be sought

The process may be summarized as follows:

I. Identification of relevant background information.
   A. Factual details of the issue at hand.
   B. Consideration of who is affected by the ethical issue.
   C. Learn and respectfully address the cultural perspectives (including applicable legal requirements) for those affected by the dilemma.

II. Identification and justification of the relevant moral rules and principles (action-guides) pertinent to the case.

III. Deliberation, through the use of moral intuition and application of ethical theory, on how to rank/balance the rules and principles pertinent to the case in order to resolve the ethical dilemma.

Case Study 8.1 Group discussion on ethical dilemma	
	A W/ro Beza, a new patient, calls the drug information center and asks Mr. Solomon, the DI pharmacist, a question. She is concerned about whether she should take the metronidazole just prescribed for her by Dr. Mark, her family practitioner (who practices at the center where the DI center is located). W/ro Beza's is approximately 8 weeks pregnant; she wonders if this medication is safe for the baby. She is being treated for a recently acquired vaginal infection. She

	states that this is the first vaginal infection that she has had in several years. She mentions that she has only recently begun seeing Dr. Mark as her family just moved into town about 3 months ago. She states that she asked him about the drug's safety, but he rather impatiently brushed off her questions by asking "don't you trust me?"
Question: What should be Mr. Solomon decision regarding Metronidazole dispensing for W/ro Beza?	

Chapter Summary

- The DI Pharmacist is responsible for the ethical and legal provision of unbiased information on medication therapies and disease state management. Hence should:
- Respect and protect the enquirer's and patient's confidentiality by safeguarding access to records, databases and reports containing patient information.
- Patient information should be shared only with authorized health professionals as needed for the care of patients.
- Adhere and practice the provision of drug information according to and in line with ethical and legal standards which should be viewed as applicable, and the DI Pharmacist should strive to meet these standards;
- Comply with relevant local/national/healthcare facility and other professional legal standards relating to the provision of drug information services.

Chapter Nine: Quality assurance of DIS

Chapter Description: This chapter is intended to enable participants to understand the basic concepts and principles of quality assurance in DIS activities. It will also equip trainees with the required attitude and skills to monitor and evaluate the activities of DIS.

Primary Objective: By the end of this chapter, participants will be able to: assure the quality of DIS.

Enabling Objectives: By the end of this chapter, participants will be able to:

- Identify components of quality assurance in DIS
- Document and report DIS activities
- Perform monitoring and evaluation of DIS activities

Chapter Outline

This chapter has the following sessions:

- Components of Quality Assurance in DIS
- Recording, Documenting and Reporting DIS activities
- Monitoring and Evaluation of DIS activities

AllocatedTime:135 minutes

9.1 Introduction

DIS aims to achieve the Quality Use of Medicines by providing and communicating timely, accurate, balanced and comprehensive information on drugs and their usage. DIS has a responsibility to provide the highest possible standard of drug information. This will include an assessment of staff performance, regular review of calls taken and answers provided, and periodic review of resources and procedures. To ensure this, a systematic process for quality monitoring, development and problem solving is required. The process should continuously identify potential improvements and document progress towards implementation.

> ***Quality assurance*** *is the set of activities that arecarried out to monitor and improve performance, so that the drug information provided is as effective and as safe as possible"*

Quality assurance (QA) activities should focus on improving the current standards set for DIS, NOT merely maintaining them. It should always start from identifying the problem and their root cause. The identified problems should be documented and reported. Routine quality activities may highlight areas of concern that require further investigation. A quality improvement (QI) program should be implemented by all centres to ensure that practice standards are met and regularly evaluated.

9.2 Components of Quality Assurance in DIS

Assessment of quality can be divided in to three major areas namely: structure, process, and outcome.

9.2.1 Structure

1. *Resources*

a) Personnel: Appropriate qualifications, familiar with all resources relevant to the center's function and additional training in DI/computer-based information systems is desirable)

b) Reference materials: Current collection of literature appropriate to the scope and nature of the services provided e.g. books, journals, drug profiles, manufacturers' literature etc.

c) Budget: Adequate funding to ensure sustainability of service.

2. *Facilities*

a) Adequate space and equipment sufficient for storage of a reference collection and provision of services.

b) Sufficient filing cabinets, shelves, desks, chairs, journal display rack, telephones, computer, access to photocopier, access to facsimile machine, etc.

c) Access to medical library, inter-library loan facilities and computer-search facilities

3. *Organization:*

a) The maintenance of a current policy and procedure manual including information and guidelines appropriate to the services provided.

b) Appropriate organogram with adequate staff

c) Appropriate hours of service: DIS services must be available during normal working hours and appropriate arrangements should be made for after-hour services.

9.2.2 Process

Process assessment reviews the activities involved in the delivery of drug informationincluding:

1. Receipt of enquiries
    a. The receipt of queries as per the SOP
    b. Completeness of enquiry forms
    c. Clarity of enquiry forms
2. Resource search and Data/information collection
    a. Availability, accuracy, credibility, appropriateness and timeliness of DI resources
    b. Depth and breadth of resources used, and the search strategy
    c. Sufficiently comprehensive
3. Evaluation and interpretation of data: retrieved information was carefully evaluated and interpreted
4. Formulation of replies
    a. Is the response correct and appropriate to the situation presented?
    b. Is the response provided promptly?
    c. Does the response completely address the question posed?
    d. Is the response communicated appropriately?
    e. Is the response clear, concise, and appropriate for the clinical situation?
    f. If follow-up was appropriate, was it provided?
5. Quality of materials produced by DIC staff (e.g., monographs, newsletters, and Continuous Education programs)
6. Documentation (forms, logbook, database)

a. Search terms, references utilized, and the availability of appropriate background or patient-specific information

b. An effective retrieval system is essential to:

- Locate previous enquiries
- Categorize the types of enquiries received
- Facilitate QI programs based on analysis of selected enquiries and failed deadlines
- Monitor workload

7. The recording processshould provide secure, long term storage and confidentiality of enquirers should be respected.

9.2.3 Outcome

Outcome assessment reviews the results of the provision of drug information.

- Enquiries should be reviewed from start to finish including data from feedback forms and surveys.
- A review of the process of outcome should be carried out at least twice yearly (preferred to do a survey at each quarter) by randomly sampling of drug information requests, monographs, and so forth.
- A minimum of 30 queries (randomly selected) should be reviewed.
- The review should be conducted by one or more people depending on the size of the centre
- Feedback forms and telephone surveys will give an indication of the service being provided.

9.3 Recording, Documenting and Reporting DIS activities

Recording

Recording is an integral part of the activities done in the process of drug information provision. The activities of the DIS should be carefully recorded and documented. Standard forms or electronic databases can facilitate recording of queries. An effective retrieval system is essential to locate previous queries, monitor workload and categorize the types of enquiries received. It can also facilitate quality assurance programs based on analysis of selected queries and failed deadlines. The recording process should provide secure long-term storage; and ensure the confidentiality of enquiries. The recorded and documented DIS activities should be reported to the relevant administrative body.

Documentation

Documentation is essential for reducing liability and potentially promoting the development of a continual service. At a minimum, the ultimate question, the materials searched, the response, and follow-up (or follow-through) should be documented. The method of documentation may be a simple form or an extensive review and summation of all processes completed. At a minimum, the ultimate question (as verified by the requestor), the materials searched (with pertinent findings noted), the response, and follow-up (or follow-through, if applicable) should be documented.

Components of documentation

Documentation of medication information requests and responses should be as per the standard form, as seen in the format below.

Table 9.1 DIS query/response documentation form

DRUG INFORMATION QUERY/RESPONSE DOCUMENTATION FORM

				Enquiry Reference No.:			
				Date of Enquiry			
Name of enquirer:			Phone No:			Email:	
Question/query:							
Drug/Product:			**Therapeutic category:**			**Indication:**	
Classification of Query:	Therapy		Pharmaceutical		Availability		
	Pregnancy		Pharmacology		Quality		
	Lactation		Pharmacokinetics		Price		
	ADR		Administration		Dose		
	Interaction		Local/Foreign equiv.		Other Specify		
Answer/ response:							
Reference sources: *(Tick appropraite)*		**References:**				**Key words:**	
* Reference books		**stoke card**				**1**	
* Journals						2	
* In-house database						3	
* Peer reviewer							
* Internet sites						**Research hours:**	
* Package inserts						0-5 mins	
* Other drug info service						5-30 mins	
* Other (please specify)						30-60 mins	
						1-4 hrs	
Response communicated by:	Oral/Verbal		Literature supplied			4-8 hrs	
	Written/print format		Internet source				
	Telephone call		Reference source				
Other material/s sent to the requester:							
							initials:
Completed By:		Date:			Time:		
Callback attempts/follow up:	1- Date:			Time:		initials:	
	1- Date:			Time:		initials:	

Rationale for documentation

- Necessary for follow-up,
- Helps in quality assessment and other performance improvement and management activities.

- Shows Characteristics of a true professional
- Demonstrates the pharmacist's commitment to patient care.
- Potential baseline for various research activities

Reporting

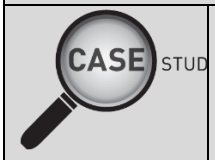
Reporting is the process of delivering the performed activities to the concerned body using standard reporting formats. All services related to DIS in a facility shall be aggregated and reported using the summary and reporting form and sent to the next administrative level. Each DIS provided in a facility will be reported to the Woreda Health office or Sub-city Health office. Period and frequency should be aligned with national Demographic and Health Information System reporting period and frequency.

Rationale for reporting

Well-functioning reporting systems in DIS enable:

- The collection and analysis of important information about the services provided,
- To improve readiness to challenges and limitations encountered,
- To improve quality of service being provided,
- Sharing the lessons learned with others health facilities
- To decide future support.

Take a close look at the summary and report form of DIS activities in Annex 9.1.

Case Study 9.1 Recording and documenting DIS activities	
	You have been assigned as the DI Pharmacist for your Health facility for a little more than a month now (January). So far, you have had 30 queries, two-third of which were walk-in enquiries from 5 of your fellow Pharmacists (all males) and the rest emailed from 4 specialist physicians (half of whom were females). The specialists all had patient-specific therapeutic enquiries on Pharmacotherapeutics, and 10 of the questions from the Pharmacists were for academic purposes (half on pharmacokinetic and half on drug interaction). You gave responses to 10 of the email queries using the same, 15 using print outs and 5 verbally; and got feedback from two of the enquirers. You utilized peer reviewed journals for the patient-specific questions and credible internet sites for the academic-related questions.

	You have so far prepared and disseminated 5 newsletters and 2 new-arrival medication updates and help organize a drug-related CPE seminar to 50 of your facility staff. You have had 25 ADR reports received from staff nurses and Clinical Pharmacists, which you have relayed to FMHACA awaiting their response. You have attended (and sometimes helped organize) all the Clinical Pharmacy weekly sessions.
Instruction/question: Complete the Summary and Reporting form provided, using the data given.	

9.4 Monitoring and Evaluation of DIS

Monitoring of DISis routine, timely tracking of the performance of DIS through continuous record-keeping, reporting or surveillance systems. Effective, frequent monitoring helps managers to make decisions in a timely manner. This allows corrective action to be taken during service provision. Monitoring indicators often show the areas that require in-depth evaluation.

Evaluation of DISis an episodic assessment of progress towards the targets. It provides feedback on whether plans had been met and, the reasons for success or failure; and should also provide directions for future plan. The purpose of indicators is to establish evidences whether inputs are producing the desired outputs and outcomes. Evaluation helps managers to determine the added value of investments in DIS. It is conducted at longer intervals and requires significant investment and conducted in a rigorous method.

A random selection of enquiries can be regularly reviewed, and feedback sought from enquirers. A common assessment tool that is used to evaluate DIS is provided in the table below (Table 9.2).

Table 9.2: Drug information response quality assurance evaluation form.

Drug Information Response Quality Assurance Evaluation Form

_____ Hospital/Health Center Region _____

Review period _____ Date of request _____

Primary Responder _____

Quality assurance milestones	Satisfactory	Unsatisfactory	Comment
Requester's demographic data was complete			
Background information inquiry was thorough and appropriate			
Search question was clearly noted			
Search strategy and reference selection were relevant and comprehensive			
Literature and information retrieved were evaluated, interpreted and documented			
Conclusions were appropriate as per the data collected and assimilated			
Oral or verbal response was accurate and complete			
Response was provided timely			
Follow-up communications were clearly documented			
Overall evaluation (circle choice)	Excellent 5 4	Acceptable 3	unacceptable 2 1
Reviewer's Recommendations :			

As a combined effort, monitoring and evaluation are used to evaluate DIS and results regularly, to determine whether progress is being made towards the targets and defined objectives. When monitoring and evaluation results show that the DIS is not meeting the targets, action must be initiated to prevent or correct problems.

Purpose of Monitoring and Evaluation

- To improve performance and achieve results.
- To measure and assess performance of DIS
- To effectively manage the outcomes and outputs known as development results.

DIS Indicators

Indicatorsare either qualitative or quantitative variables that measure the extent of progress in the level of performance.

Description of indicators

There are various indicators used to measure the level of performance of DIS activities. The first three indicators mentioned below are included in the national Pharmaceuticals Supply Chain Management, Pharmacy Service and Medical Equipment management. The assessment of these indicators is done by administrative bodies like Woreda Health Office (WoHO), Sub-city Health Office (ScHO) and Zonal Health Department (ZHD) and will be reported to higher level. The last four indicators will be assessed and used by the health facility for their own consumption and to improve DIS activities.

Table 9.3 Indicators to measure performance of DIS activities.

1. Health facilities with functional DIS
Definition: Percentage of health facilities (HFs) that have functional drug information services.
Formula $\frac{\text{Number of Health facility with functional DIS}}{(Total\ number\ of\ health\ facilities\ )}\ x\ 100$
Purpose and Issues This indicator shows the overall functionality of Health facilities as compared to the total number of HFs. The indicator gives the percentage of 'active' facilities with respect to the provisionof DIS. to health professionals, patients and general public.

The presence of functional DIS is expressed in terms of availability of dedicated room, dedicated pharmacy professional, adequate reference materials and equipment, standard operating procedures, sample query response forms completed, medicine education program and report, sample alerts/newsletters prepared, action plan and performance reports. A health facility DIS is considered functional when a minimum of 80% score is achieved using a checklist.

Data Source

- Survey, direct observation of DIS

Frequency: every quarter

Target: 100%

Responsible: WoHO/ ScHO/ZHD

2. HFs with minimum package of DIS reference materials, equipment and furniture

Definition:

Number of health facility with minimumpackage of drug information reference materials,equipment and furniture

Formula: Number of DIS with minimum package of reference materials, equipment and furniture out of the total DIS.

Purpose and Issues

This indicator measures quality of functional DIS. The DIS should have a dedicated room that has sufficient space and appropriate furniture and equipment including telephone, computer, printer, filing cabinets and internet access. It should also have a collection of updated national and international authoritative reference materials such as books, journals, guidelines, formularies, and databases.

Data Source

- Survey, direct observation of DIS

Frequency: Quarterly

Target: 100%

Responsible: WoHO/ ScHO/ZHD

3. Percentage of DIS units that provide medicine use education to clients

Definition:

Percentage of drug information service which provide education for the patients on rational use of medicines through different mechanisms for appropriateness of therapy

Formula $\frac{\text{Number of DIS units that provide medicine use education to clients}}{(Total\ number\ of\ DIS\ in\ health\ facilities\ )}\ x\ 100$

Purpose and Issues

This indicator measures the percentage of HFs that provide medicine use education to patients/clients. The appropriate information provided to the patient about the medicines they use will help in achieving optimum adherence that results in better treatment outcomes. Medicine use education is needed so that people have the skills and knowledge to make informed decisions about how to use and store medicines and to understand the role of medicines in health care, with their potential benefits and risks.

Data Source

- Survey, Medicine use education reporting form

Frequency: Quarterly

Target: 100%

Responsible: WoHO/ ScHO/ZHD

4. Percentage of managed drug information queries

Definition:

Percentage of managed drug information queries is the number of drug information response formulated and communicated against the total DI queries

Formula $\frac{\text{Number of drug information response formulated and communicated}}{(Total\ number\ of\ queries\ received\ )}\ x\ 100$

Purpose and Issues

This indicator shows the activity of drug information service in the health facility with respect tothe appropriate response to drug information queries.

The service generally responds to drug information queries received from the health care team or clients.

Data Source

- Summary and reporting form
- DI Request and Response Forms

Frequency: Monthly

Target: 100%

Responsible: DIS coordinator, Pharmacy Head

5. Number of publication issued

Definition:

Number of publications issued in response to drug alerts/newsletter, therapy updates and monographs, etc.

Formula: Total number of publications made during the quarter

Purpose and Issues

This indicator shows the activity of DISin the health facility through the preparationand the dissemination of DI in the form of drug alerts, bulletins, newsletters, therapy updates, monographs, new arrival or availability, and other publications.

The service generally emanates from DIS to update other health care workers and the public on recent updates related to drugs.

Data Source

- Summary and reporting form

Frequency: Quarterly

Target: 3 publications (newsletter, drug alert, therapy update, or monograph)

Responsible: DIS coordinator, Pharmacy Head

6. Number of Adverse Drug Event reported

Definition:

Number of adverse drug event (ADE) reported to FMHACA

Formula: Total number of ADE reported during the time period

Purpose and Issues

This indicator shows the activity of the DIS in the health facility in reporting ADE to FMHACA to contribute to the national pharmacovigilance system.

The DIS reports any untoward medical occurrence. This will equip FMHACA with the safety profile of the drugs and support the decisions to make informed decisions.

Data Source

- Summary and reporting form

Frequency: Quarterly

Target:

Responsible: DIS coordinator, Pharmacy Head

7. Documentation performance

Definition:

Percentage of DIS activities documented appropriately

Formula: $\frac{\text{Number of DI activities performed AND documented during the quarter}}{(Total\ number\ of\ DI\ activities\ planned\ during\ the\ quarter)}\ x\ 100$

Purpose and Issues

This indicator shows the percentage of DI activities (Responding to queries, Publishing of DI materials and Organizing of Continuous Pharmacy Education events) performed AND documented appropriately as compared to the respective activities planned during a specific quarter. It provides a better picture when calculated for each activity separately.

Data Source

- Annual action plan, Documentation form

Frequency: Quarterly

Target: 100%

Responsible: DIS coordinator and/or Pharmacy Head

8. Reporting performance

Definition:

Percentage of DIS activities reported to the concerned body in time

Formula: $\frac{\text{Number of DI activities reported timely during the quarter}}{(Total\ number\ of\ DI\ activities\ documented\ during\ the\ quarter)}\ x\ 100$

Purpose and Issues

This indicator shows the percentage of DI activities (Responding to queries, Publishing of DI materials and Organizing of Continuous Pharmacy Education events) reported in a timely manner, as compared to the DI activities documented during a specific quarter. It provides a better picture when calculated for each activity separately.

Data Source

- Reporting form, Documentation form

Frequency: Quarterly

Target: 100%

Responsible: DIS coordinator and/or Pharmacy Head

Case Study 9.2 Group exercise on DI indicators	
 .	You wanted to use the data from the Summary and Report form you filled out earlier to see if you have made progress in your performance in the quarter. Assume that the same numbers were replicated for the next 3 months and that you have appropriately documented and reported the DIS activities. You had an initial plan to help organize 2 CME events in each quarter
Calculate the following indicators: ▪ *Percentage of managed DI queries* ▪ *Documentation performance for the CPE event* ▪ *Reporting performance for the publishing of DI materials*	

Chapter Summary

- Quality assurance activities should focus on improving the current standards set for DIS.
- Assessment of quality can be divided in to three major areas namely; structure, process and outcome.
- The activities of DIS should be carefully documented and reported to the next administrative level.
- Performining Monitoring and evaluation to evaluate DIS.

Chapter Ten: Getting Started

Chapter Description: This chapter enables the participants to discuss on getting a DIS started from the beginning or improving a DIS that has only limited activity.

Primary Objective/s: At the end of this chapter participants will be able to establish and revitalize DIS at health facilities.

Enabling Objectives: By the end of this chapter, participants will be able to:

- To discuss the basics of starting a DIS where none exists
- To improve the functioning of an existing DIS
- Prepare draft action plan to establish or revitalized DIS

Chapter Outline:

This chapter has the following outlines:

- Stepwise approach to start provision of Drug Information Service
- Revitalizing non-functioning Drug Information Service
- Planning to establish/revitalize DIS

Allocated Time:125 minutes

10.1. Addressing the Problem

The way to get started will depend on the various circumstances and context the health facilities. Many hospitals and health centers do not have DIS. Where DIS do exist, they may not function properly. Any process of change requires, first, that someone realizes the need for change. In the context of DIS, the first step is, to realize that lack of access to up-to-date, unbiased, and objective information on medicines is a problem and that provision of drug information service at each health facility will provide a framework for solving the problem. Thereafter, convince others of the need to address the problem and to work on establishing new DIS or functioning existing DIS at health facilities.

10.1.1. Stepwise approach to start provision of drug information service where none exists

The Ethiopian Drug Policy, the Hospital Services Transformation Guideline (EHSTG), health centers reform implementation guidelines (EHCRIG) and consider provision of current, evidence based and unbiased drug information service as compulsory requirement. This could be a good beginning to initiate the establishment of DIS at health facilities.

Activity 10.1 Reflection points on steps in establishing DIS	
	**What steps will you follow to establish DIS at your health facility**

Table 10.1 Stepwise approach to start provision of drug information service where none exists

Step	Approach
Step 1:	Starting a DIS will require undertaking a lot of advocacy. For this you will be better prepared to gather evidence to show the needs for drug information, and the existing situation in the health facility. You further use the guidelines and standards as mandatory requirement for the establishment of DIS.
Step 2:	Discuss on the importance of provision of drug information service with the health facility management. You can demonstrate the role of DIS in various activities of the health facility. The information and skills acquired in this training will serve as an input while explaining/demonstrating the DIS activities.
Step 3:	Orient health facility staff with the approval from health facility management, organize

	orientation for department heads and other relevant staff. Explain briefly the importance, role and structure of DIS. The DIS SOP manual and the materials collected from this training can be used as a main reference for the orientation.
Step 4:	Present the draft plan you prepared during this training and establish consensus with the health facility management and health providers and initiate provision of drug information service using the available resource. You can start the service provision by implementing some of the DIS functions that do not require resource. These include, provision of medicine use education, issuing updates on new arrivals, overstock and near expiry items, and facilitating ADE reporting etc.
Step 5:	Revise your plan of action, develop /adopt SOP for DIS activities and secure approval from the health facility DTC.
Step 6:	While providing drug information service using available resources, seek for potential sources to fulfill the required materials for smooth functioning of DIS. You may prepare and submit to the health facility management to avail the required materials by own or communicate donors.
Step 7:	follow the progress of your proposal. As soon as all required facilities and materials secured, officially launch the provision of Drug Information Service at the health facility.

Record, report and document all activities performed at all steps

10.1.2. Stepwise approach in revitalizing non-functioning Drug Information Service

When the established Drug Information Service don't function properly revitalizing the service provision is the main remedy as soon as possible. For the DIS to be said functional it should at least fulfill the following minimum requirements:

1. Separate room assigned to DIS
2. DIS focal person assigned with official letter
3. Has SOP approved by the health facility DTC/management.
4. Has current action plan with primary DIS functions
5. Undertaking activities based on current action plan
6. Regularly record, report and document DIS activities

If the DIS failed to fulfill the above-mentioned requirements, we can say the DIS is poorly functional. Therefore, revitalizing the DIS should be initiated. Steps to be followed in the process are listed below.

Table 10.2 Stepwise approach in revitalizing non-functioning Drug Information Service

Step	Approach
Step 1:	Identify possible causes: The possible causes why the DIS ceases or not-functioning well may vary from facility to facility and each facility should asses its own causes. Possible causes could be: • Lack of awareness of amongst health facility staff and management • Lack of commitment • Lack of support from health facility management. • High work burden for DIS pharmacist to undertake DIS activities
Step 2:	Prioritize the identified problems and understand the root causes: This is a crucial step in the process of revitalizing the DIS since it can help to know the root causes which will lead to the solution.
Step 3:	Prepare the draft plan for revitalizing DIS: The draft plan of revitalization should be based on the problems identified and prioritized.
Step 4:	Presenting draft plan to revitalize DIS for the management: The draft plan of revitalization should be communicated and discussed with the health facility DTC so that the DTC and management could approve the plan of revitalization and support the process.
Step 5:	Revitalize the DIS based on the approved plan of revitalization: Start the revitalization by providing orientation to the staff through various means.

10.2. Promotion and Advocacy of Drug Information Services

Advocacy is the deliberate process of influencing those who make policy decisions.

With the profession of pharmacy changing dramatically, it has become apparent the promotion of skills and services to health care providers and clients. It is important that DI pharmacists advocate for their scope of practice and promote their role and value in the management of medication therapy through the provision of drug information services. The DI pharmacists need to be taking responsibility for advocating through the interactions with health care professionals, patients, and the community. They can apply verbal and non-verbal communication tools to increase awareness about who they are, what they do and what they can do. Following are some of the tools that DI pharmacists can use in promoting their practice.

- Organizing or attending conferences/sessions (DTC/morning/rounds/CME)
- Making a phone call or visit to introduce self and explain your practice to health providers
- Counselling patients
- Create Alerts, poster or pamphlet describing the services
- Business card, information sheet or note about the service
- Identify self (by wearing a name tag that includes your title)
- Newsletters and other widespread promotional communication.
- Email, Website or social media pages
- Opinion leaders

N.B.A single advocacy/promotional method may rarely result in suitable changes, a mix of methods may be preferred.

Plan to establish/revitalizing non-functioning Drug Information Service

Activity 10.2 Individaul Exercise on planning	
	Prepare draft plan of action to establish or revitalize DIS at your facility. Use the planning template annexed.

Chapter Summary

- The goal of provision of DIS is to ensure that patients are provided with the best possible quality of therapeutic care.
- Getting a DIS started or making it functional will require a strategy based on: Political and administrative support, local conditions, local data, starting small and then scaling up, handling a problem that can easily be addressed.

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Annexes

Annex 2.1. Useful tertiary and secondary resources for common categories of drug information

Type of Request	Useful Tertiary Sources	Secondary Resources
General Product Information	Major compendia*, Handbook of Nonprescription Drugs, product labeling.	MEDLINE®, EMBASE®, IPA, IDIS
Adverse Effects	Meyler's Side Effects of Drugs, Side Effects of Drugs Annual, product labeling, major compendia*	Reactions Weekly, MEDLINE®, EMBASE®, IPA, IDIS
Availability of Dosage Forms	Red Book, American Drug Index major compendia*	_____
Compounding/Formulations	Remington: The Science and Practice of Pharmacy, Merck Index, A Practical Guide to Contemporary Pharmacy Practice, USP/NF, Trissel's Stability of Compounded Formulations, Extemporaneous Formulations, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, USP Pharmacists' Pharmacopeia	IPA, IDIS, EMBASE®, MEDLINE®
Dietary Supplements	Natural Medicine Comprehensive Database, Review of Natural Products, Natural Standard, PDR for Herbal Medicine, Trease and Evans' Pharmacognosy	EMBASE®, MEDLINE®, IPA, IDIS
Dosage Recommendations	Major compendia*, Drug Prescribing in Renal Failure	MEDLINE®, IPA, IDIS, EMBASE®
Drug Interactions	Hansten and Horn's Drug Interaction Analysis and Management, Drug Interaction Facts, Stockley's Drug Interactions, Food-Medication Interactions, Drug Therapy Monitoring System, major compendia*	Reactions Weekly, IPA
Drug-Laboratory Interference	Basic Skills in Interpreting Laboratory Data, Laboratory Tests and Diagnostic Procedures	
Geriatric Dosage Recommendations	Geriatric Dosage Handbook, major compendia*	MEDLINE®, IPA, IDIS, EMBASE®
Identification of Product	Identidex, Clinical Pharmacology, Drugs.com, IDENT-A-DRUG, Lexicomp, Facts & Comparisons® eAnswers	
Investigational Drug Information	FDA Web site (http://www.fda.gov), Clinicaltrials.gov, MedlinePlus, manufacturer Web sites	Current Contents, EMBASE®, MEDLINE®, LexisNexis®, IPA, IDIS
Incompatibility/Stability	Handbook of Injectable Drugs, King Guide to Parenteral Admixtures, Trissel's 2 Clinical Pharmaceutics Database, Extended Stability for Parenteral Drugs, Trissel's Stability of Compounded Formulations, Remington: The Science and Practice of Pharmacy	IPA, IDIS, EMBASE®, MEDLINE®
International Drug Equivalency	Martindale: The Complete Drug Reference, Index Nominum, Internet Search Engines, Specific country resources	

Method/Rate of Administration	Major compendia*	
Pediatric Dosage Recommendations	The Harriet Lane Handbook, Pediatric and Neonatal Dosage Handbook, Neofax, major compendia*	MEDLINE®, IPA, IDIS, EMBASE®
Pharmacokinetics	Basic Clinical Pharmacokinetics, Applied Biopharmaceutics and Pharmacokinetics, major compendia*	IPA, EMBASE®, MEDLINE®, IDIS
Pharmacology	Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Basic & Clinical Pharmacology, Brody's Human Pharmacology: Molecular to Clinical, Principles of Pharmacology	IDIS, IPA, EMBASE®, MEDLINE®
Pharmacy Law	Pharmacy Practice and the Law, Guide to Federal Pharmacy Law, State Board of Pharmacy Web sites	LexisNexis®
Teratogenicity/Lactation	Drugs in Pregnancy and Lactation, Medications and Mother's Milk, Catalog of Teratogenic Agents, Drugs during Pregnancy and Lactation, REPRORISK, major compendia*	Reactions Weekly, EMBASE®, MEDLINE®, IDIS, IPA
Therapy Evaluation/Drugs of Choice	Pharmacotherapy: a Pathophysiologic Approach, Pharmacotherapy Principles and Practice, Applied Therapeutics: The Clinical Use of Drugs, The Merck Manual of diagnosis and therapy, Harrison's Principles of Internal Medicine, Goldman's Cecil Medicine, Textbook of Therapeutics, Conn's Current Therapy, Medscape	MEDLINE®, EMBASE®, IDIS, IPA
Toxicology Information	POISINDEX®,Goldfrank's Toxicologic Emergencies, Casarett & Doull's Toxicology: The Basic Science of Poisons, Poisoning & Toxicology Handbook, Haddad and Winchester's Clinical Management of Drug Overdose, TOXNET	Reactions Weekly, EMBASE®, MEDLINE®, IPA, IDIS, BIOSIS
*Facts & Comparisons®, AHFS Drug Information®, Physicians' Desk Reference® (PDR), Micromedex, Lexicomp®, and Clinical Pharmacology are considered as major compendia.		

Annex 2.2. Questions for evaluation of information sources

Evaluating information sources

Questions to ask when reviewing original clinical articles

- In which journal was the article published? What is the reputation of the journal? Is it known to have high standards for the acceptance of articles? Are articles peer reviewed?
- Who is the author, and what is his or her affiliation?
- Does the article report the results of a properly designed clinical study, or is it based on case reports or observations? If a clinical study, what was the sample size, and how were participants selected? Were controls used? Was the study prospective or retrospective? Is the report adequately referenced?
- Are reasonable conclusions drawn?
- Who funded the study? Does any potential exist for conflict of interest?

Questions to ask about bibliographic, abstracting, or indexing services

- What journals or information resources are covered by the service, and are these resources the ones that are essential for the particular purpose?
- What is the lag time between the publication of a journal and its inclusion in the service?
- How easily can the service be used? Are key words indexed? Are subject headings used?
- If abstracts are provided, who develops the abstracts, and how accurately do they reflect the primary source?

Questions to ask about consensus-generated documents

- How is consensus defined, and how are the individuals participating in the consensus definition process selected?
- How good is the consensus-generation process?
- Are references provided and accessible?
- Is the consensus process open to public review and comment?
- Is the information based on evidence published in peer-reviewed literature, or is it simply a compilation of use patterns reported as being accepted by the medical community?
- When was the consensus document published, and how frequently is the information updated?
- Who published the information, and what kind of reputation does the publisher have?

Questions to ask about secondary and tertiary references written by individuals or groups of individuals

- Who is the author, and what are his or her qualifications?
- Who is the publisher, and what is its reputation?
- Who paid for the development of the information? Does it come from a special-interest group? If the publication is reporting proceedings from a conference, who organized the conference, and do the organizers have a special interest?
- Has the information been peer reviewed? How good is the peer-review process?
- When was the information developed, and how current is it?
- Are references included in the article, or can the references be accessed by other means?

Source: MSH-WHO; Managing Access to Medicines and Health Technologies, MDS-3 3rd ed, Chapter 34, Medicine and therapeutics information, Dec 2012 pp 34.4. Accessed on 01/17/2018

https://www.msh.org/resources/mds-3-managing-access-to-medicines-and-health-technologies

Annex 2.3 Checklist to appraise systematic literature review

Milestones	Result
Clear review question stated (question type, population, intervention, and outcome)?	
Included study designs stated?	
Criteria used to assess the quality of studies	(List:)
Study characteristics documented for included studies?	
Inclusion/exclusion criteria stated?	
Literature search strategy recorded?	
Data abstracted in a manner consistent with the review question?	
Reproducible and bias-free process of — identifying studies? — including studies? — abstracting data?	
Relevant, justifiable bottom line?	
Meta-analysis for different outcomes used (appropriately)?	
Up to date?	

ANNEX 2.4 Questions for Assessing Clinical Trials

Overall Assessment

- Was the article published in a reputable, peer-reviewed journal?
- Are the investigator's training/education/practice site adequate for the study objective?
- Did the funding source bias the study?

Title/Abstract

- Was the title unbiased?
- Did the abstract contain information not found within the study?
- Did the abstract provide a clear overview of the purpose, methods, results, and conclusions of the study?

Introduction

- Did the authors provide sufficient background information to demonstrate the rationale for the study?
- Were the study objectives clearly identified?
- What was the major null hypothesis and alternate hypothesis?

Methods

- Was an appropriate study design used to answer the question?
- Were reasonable inclusion/exclusion criteria presented to represent an appropriate patient population?
- Was a selection bias present?
- Was subject recruitment described? If so, how were subjects recruited? Was it appropriate?
- Was institutional review board (IRB) approval obtained?
- Was subject informed consent obtained?
- Were the intervention and control regimens appropriate?
- What type of blinding was used? Was this type appropriate?
- Was randomization included? If so, what type was used? Was this appropriate?
- Who generated the allocation sequence, enrolled participants, and assigned participants to groups? Was this appropriate?
- Which ancillary treatments were permitted? Would they have affected the outcome?
- Was a run-in period included? How does this affect the results?
- Did the investigators measure compliance? How was compliance measured? Was this adequate?
- Was the primary endpoint appropriate for the study objective?
- Were secondary endpoints measured? If so, were they adequate for what was being studied?
- Were planned subgroup analyses planned? If so, were they appropriate?
- Was the method used to measure the primary endpoint appropriate?
  What type of data best describes the primary endpoint? Is this what was gathered?
- Were data collected appropriately?

- What number of patients was needed for the primary endpoint to detect a difference between groups (power analysis)? Was the necessary sample size calculated? Were there enough patients enrolled to reach this endpoint?
- What were the alpha (α) and beta (β) values? Were these appropriate?
- Were the statistical tests used appropriate?

Results

- Were the number of patients screened, enrolled, administered treatment, completing, and withdrawing from the study reported? Were reasons for subject discontinuations reported? Were withdrawals handled appropriately?
- Was the trial adequately powered?
- Were the subject demographics between groups similar at baseline? If not, were the differences likely to have an affect on the outcome data?
- Were data presented clearly?
- Were the results adjusted to take into account confounding variables?
- Was intention-to-treat analysis used?
- Were estimated effect size, p values, and confidence intervals reported?
- Were the results statistically significant? Clinically different?
- Based on the results, could a Type I or Type II error have occurred?
- Can the trial results be extrapolated to the population?
- Was the null hypothesis accepted or rejected?
- Are subgroup analysis presented? Are these appropriate?
- Was ancillary therapy included? Did this affect the study results?
- Were therapy adverse effects included?

Conclusions/Discussion

- Did the information appear biased or did the trial results support the conclusions?
- Were trial limitations described?
- Did the investigators explain unexpected results?
- Are the results able to be extrapolated to the population?
- Were the study results clinically meaningful?

References

- Were the references listed well represented (e.g., current and well representing the literature)?
- Is a comprehensive list of published articles related to the trial objective presented?

Annex 2.5 Article for review 1 (Activity 2.1)

Effect of preventive treatment for tuberculosis in adults infected with HIV: Systematic review of randomized placebo controlled trials

David Wilkinson, S B Squire, Paul Garner(*BMJ* 1998;317:625–629. Reproduced with permission from the BMJ Publishing Group).

Abstract

Objective: To determine whether preventive treatment for tuberculosis in adults infected with HIV reduces the frequency of tuberculosis and overall mortality.

Design: Systematic review and data synthesis of randomised placebo controlled trials.

Main outcome measures: Active tuberculosis, mortality, and adverse drug reaction requiring cessation of the study regimen. Outcomes stratified by status of purified protein derivative skin test.

Results: Four trials comprising 4055 adults from Haiti, Kenya, the United States, and Uganda were included. All compared isoniazid (6–12 months) with placebo, and one trial also compared multidrug treatment for 3 months with placebo. Mean follow up was 15–33 months. Overall, frequency of tuberculosis (relative risk 0.57, 95% confidence interval 0.41 to 0.79) was reduced in those receiving preventive treatment compared with placebo: mortality was not significantly reduced (0.93, 0.83 to 1.05). In subjects positive for purified protein derivative receiving preventive treatment, the risk of tuberculosis was reduced substantially (0.32, 0.19 to 0.51) and the risk of death was reduced moderately (0.73, 0.57 to 0.95) compared with those taking placebo. In adults negative for purified protein derivative receiving preventive treatment, the risk of tuberculosis (0.82, 0.50 to 1.36) and the risk of death (1.02, 0.89 to 1.17) were not reduced significantly. Adverse drug reactions were more frequent, but not significantly so, in patients receiving drug compared with placebo (1.45, 0.98 to 2.14).

Conclusions: Preventive treatment given for 3–12 months protects against tuberculosis in adults infected with HIV, at least in the short to medium term. Protection is greatest in subjects positive for purified protein derivative, in whom death is also less frequent. Long term benefits remain to be shown.

Introduction

Strategies to control tuberculosis comprise case treatment, preventive treatment, and vaccination with BCG, with the expectation that improved socioeconomic conditions will lead to a decline in disease incidence.[1,2] Preventive treatment aims to eradicate latent infection with *Mycobacterium tuberculosis* before active disease develops. Latent infection is shown by a positive reaction to intradermal injection with purified protein derivative (tuberculin skin test). Trials in people with tuberculosis infection but not infected with HIV have shown that isoniazid given for 6–12 months substantially reduces the incidence of active tuberculosis.[3]

Infection with HIV has changed the natural history of infection with *M tuberculosis*.[4] People who are infected with HIV and who have a positive tuberculin skin test have a 30% or more lifetime risk of developing active tuberculosis,[5] and tuberculosis is the most common HIV related disease in developing countries.[1,4] Thus, preventive treatment may be an important intervention to reduce the burden of tuberculosis in people infected with HIV, and their contacts, but its efficacy cannot simply be extrapolated from studies in people not infected with HIV.

As several fairly small trials have been done, we conducted this systematic review to summarise the evidence available to date as to whether preventive treatment for tuberculosis is effective in reducing the incidence of active tuberculosis and of death.

Subjects and methods

Criteria for selecting studies for review

We included only randomised controlled trials that compared drug regimens aimed at preventing tuberculosis with placebo. Trials were considered irrespective of setting or target group, and we included all different drug regimens tested. Preventive treatment was defined as tuberculosis chemotherapy given to people who have a particular risk of

developing tuberculosis. Particular risk refers to people who are infected with HIV and either infected with *M tuberculosis* (positive for purified protein derivative), or who are negative for purified protein derivative but live in a community where tuberculosis is endemic, or have a high risk of infection.[6] Our definition of negative for purified protein derivative allowed inclusion of anergic patients (defined as a skin test reaction of < 5 mm to 5 tuberculin units, and < 2 mm reaction to mumps, tetanus toxoid, and candida antigen). In some instances we were unable to stratify outcomes by anergy in subjects negative for purified protein derivative as not all trials tested for it.

Search strategy

We searched Medline using the search terms HIV, tuberculosis, preventive therapy, and chemoprophylaxis.We also searched the Cochrane Controlled Trials Register, the most comprehensive source of controlled trials (disk issue 1, 1998).[7] In addition, we searched references of all retrieved articles and contacted relevant researchers to ensure that all completed trials had been identified.

Review procedure

Trials considered for inclusion were examined to determine completeness of reporting. One of us (DW) collated data on study methods, participants, interventions, and outcomes for each study, and another (PG) checked the collated data. Authors of incomplete or abstracted trials were contacted for further details. The quality of each trial was graded using predefined criteria, assessing method of allocation sequence generation, allocation concealment, inclusion of all randomised participants, follow up of subjects, and analysis by intention to treat.

Outcome measures

The outcome measures were (a) frequency of active tuberculosis, defined microbiologically (preferably by culture) or histologically, or as a clinical syndrome consisting of typical symptoms, independently assessed chest x ray, and a documented response to treatment,[8] (b) frequency of mortality, and (c) occurrence of adverse drug reaction (defined as a reaction resulting in cessation of the study drugs). Where possible, outcome measures were stratified by purified protein derivative status (positive, negative, and unknown). Owing to the

Table 1 Characteristics of randomised placebo controlled trials of preventive treatment for tuberculosis in adultsinfected with HIV included in review

Study (country)	Method	Participants	Interventions	Outcomes
Pape et al[9] (Haiti)	Randomised by computer Allocation not described Double blind*	Symptom free, newly diagnosed (n=118) No active tuberculosis (91/118 (77%) were women) Positive or negative for tuberculin†	Isoniazid 300 mg daily for 12 months	Subjects assessed every 3 months Mean follow up 33 months No loss to follow up
Hawken et al[10] (Kenya)	Block randomised by computer Allocation concealed Double blind‡	Mostly symptom free (n=684) No active tuberculosis Positive or negative for tuberculin	Isoniazid 300 mg daily for 6 months	356/509 (70%) of expected subjects seen at the end of the trial Median follow up 20 months
Gordin et al[11] (USA; 74% New York)	Randomisation not described Allocation concealment not described No data on number of eligible patients not enrolled	HIV infected (119/517 (23%) had AIDS) Negative for tuberculin Anergic At high risk of tuberculosis	Isoniazid 300 mg daily for 6 months	326 (63%) patients completed treatment 6% and 7% of treatment and placebo groups were lost respectively Mean follow up 33 months

Whalen et al[12] (Uganda)	Block randomised by computer (n=2736) Allocation concealedß Double blind	Mild HIV disease Positive for tuberculin Anergic	Isoniazid 300 mg daily for 6 months then isoniazid plus rifampicin 600 mg daily for 3 months then isoniazid plus rifampicin plus pyrazinamide 2 g for 3 months Anergic: isoniazid 300 mg daily for 6 months	80–89% of the different groups completed the trials No data on follow up procedures Mean follow up 15 months

* Tuberculin as purified protein derivative.

21 of 60 patients in placebo arm accepted offer of isoniazid at time of interim analysis, but all were analysed in placebo arm.

12 of 696 enrolled patients were excluded and 14 of 684 failed to return after recruitment.ß 9095 people were screened; 4306 (47%) did not complete baseline investigations and 2053 (23%) were ineligible.

small number of subjects with unknown purified protein derivative status no stratum specific analysis of this group is reported.

Statistical analysis

We used the Mantel–Haenszel method to calculate summary statistics (relative risk and 95% confidence interval). A fixed effects model was used, and results were little different when using a random effects model. All analyses were done with Revman 3.0.1. (Update Software, Oxford).

Results

Included trials

Of seven identified trials, four were eligible for inclusion in this review.[9–12] Of the remaining three, one was reported to be incomplete after contacting the investigators,[13] one compared two different drug regimens,[14] and a third had not yet been published – the authors declined inclusion of their data in our review.

Exclusion criteria were similar in all trials and included past history of tuberculosis, current tuberculosis, pregnancy, abnormal liver enzymes, and serious intercurrent illness. All treatment was self administered and adherence was monitored variously through self reporting, attendance at scheduled clinic appointments, and urine testing (both routine and unscheduled). No data on adherence were reported by Pape et al;[9] Hawken et al reported that 31% of subjects missed at least 5 weeks' preventive treatment, and 70% had at least 50% positive urine tests;[10] Gordin et al reported that only 63% of patients completed preventive treatment within 6 months;[11] and Whalen et al reported that 75% of scheduled and 80% of unscheduled urine tests were positive.[12] Follow up was generally short, ranging from an average of 15 to 33 months (table). All trials were analysed by intention to treat.

The figure summarises the outcomes of the four trials. Overall, the frequency of tuberculosis was reduced in subjects who received preventive treatment compared with those who received placebo (relative risk 0.57, 95% confidence interval 0.41 to 0.79). Risk of death (0.93, 0.83 to 1.05) was not significantly different in the two groups.

In two trials, when comparing subjects positive for purified protein derivative who received preventive treatment with those who received placebo, the 95% confidence interval for the relative risk of both tuberculosis and mortality included one (fig), indicating non-significant results. The pooled risk of tuberculosis in those receiving preventive treatment compared with placebo was 0.32 (0.19 to 0.51), indicating substantial protection against active disease. The pooled relative risk of mortality was 0.73 (0.57 to 0.95), indicating a moderate reduction in the risk of death in those receiving preventive treatment. Hawken et al did not define adverse drug reaction by purified protein derivative status and thus no stratified analysis of this outcome measure is reported here.[10]

In adults with a negative tuberculin skin test the estimates of effect in all trials included one, indicating non-significant results (fig). The pooled risk of tuberculosis in subjects with a negative tuberculin skin test who received preventive

treatment was 0.82 (0.50 to 1.36) compared with placebo, confirming that no substantial protection was conferred by the intervention. Similarly, the pooled relative risk for mortality was 1.02 (0.89 to 1.17) confirming that no substantial protection was conferred by the intervention.

Overall, adverse drug reactions were more common, but not significantly so (1.45, 0.98 to 2.14), in patients receiving active drug (86/2551; 3.4%) compared with those receiving placebo (43/1386; 3.1%).

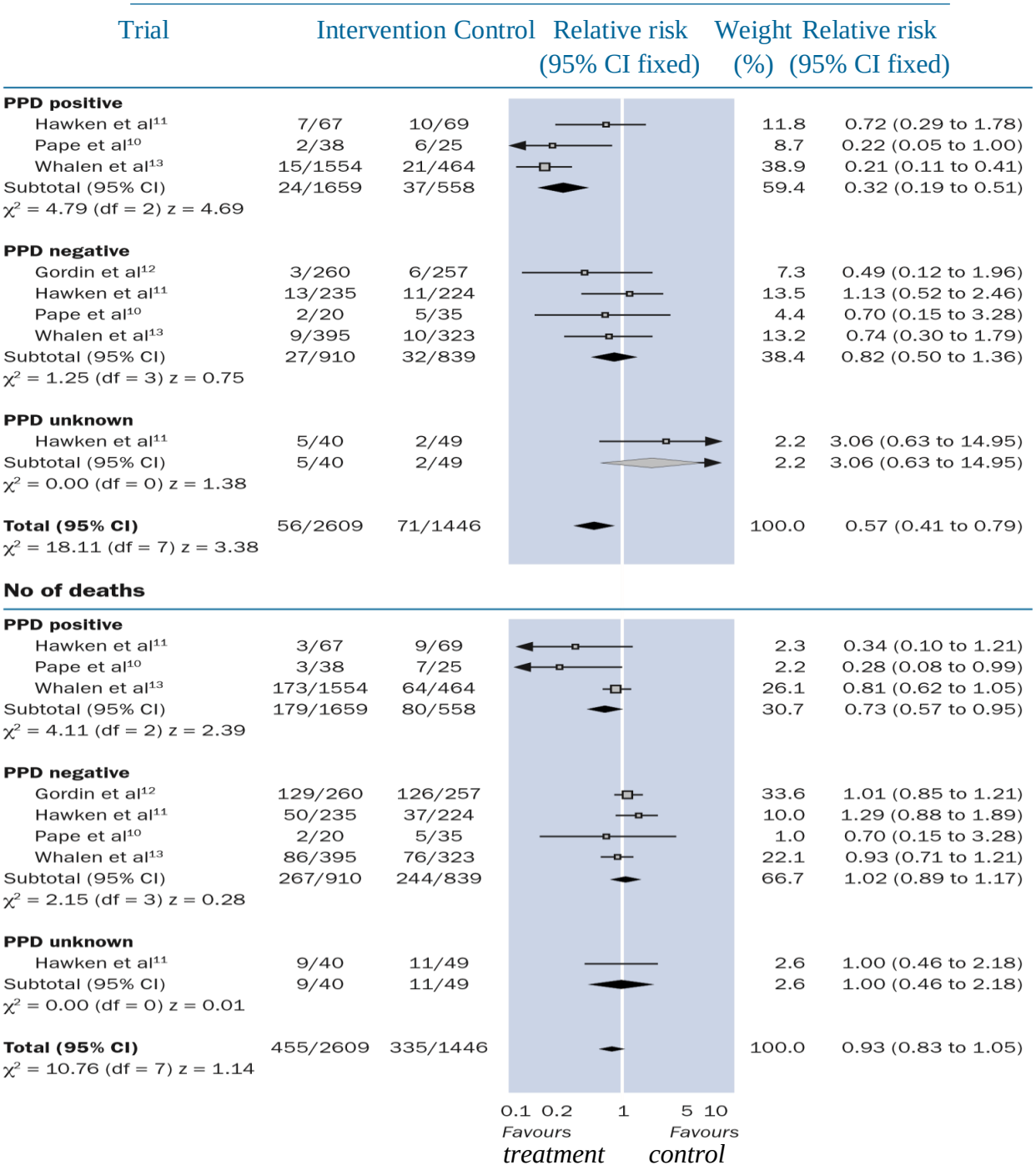
Discussion

Available evidence to date indicates that preventive treatment reduces the frequency of active tuberculosis in adults infected with HIV by approximately half. Protection against tuberculosis is greatest in adults infected with HIV who have a positive tuberculin skin test (approximately 70% reduction), and reduced incidence of mortality is also observed in this group (approximately 25%). Average follow up in these trials was 15 to 33 months, and it is not possible to conclude that benefit persists beyond this time. A small and non-significant reduction in tuberculosis incidence was observed in adults with a negative tuberculin skin test, and no effect on mortality was observed in this group.

Thus, in settings where testing for purified protein derivative is possible, preventive treatment might best only be offered to adults infected with HIV with a positive tuberculin skin test. In settings where testing for purified protein derivative is not possible, if preventive treatment is given to all adults infected with HIV, it is likely that the frequency of tuberculosis will still be reduced, but to a smaller extent.

Our review shows the value of systematic review and meta-analysis. Most of the trials studied were underpowered and reported results of borderline significance. By combining data we are able to provide more precise estimates of effect for the main outcome measures. The direction of effect of the intervention in the different settings was the same (fig), supporting the validity of combining data. A meta-analysis of individual patient data would

No with active tuberculosis



Effect of preventive treatment for tuberculosis in adults infected with HIV on active tuberculosis and mortality, stratified by purified protein derivative status

be required to provide summary estimates of measures such as time to disease and death, and efforts to gather data to conduct such an analysis are under way.

Possible biases

A systematic review may be biased if trials reporting negative findings are not published. The trial reported to be incomplete[13] published positive findings in abstract form, and the trial in preparation has also reported positive results. We found no statistical evidence of heterogeneity in this meta-analysis, but the power to detect heterogeneity was

limited by the small number of trials. While there seems to be some clinical heterogeneity (fig) this tends to be limited to one trial in each subgroup, and varying levels of adherence in the different trials might explain this, at least in part.

It may be difficult to generalise our findings to all populations, as the baseline risk of tuberculosis varied substantially by setting. Gordin et al observed a very much lower incidence of tuberculosis than expected.[11] Preventive treatment works mainly by preventing reactivation of latent infection. Recent infection may account for 30–40% of the burden of tuberculosis in both developed[15] and developing

countries.16 The relative importance of these two mechanisms may vary by setting and is likely to influence effectiveness of preventive treatment. When given for only a few months, there is little opportunity for preventive treatment to protect against exposure to infection with *M tuberculosis* in adults negative for purified protein derivative. Adults positive for purified protein derivative are at risk of new infection after preventive treatment has been stopped.

Key messages

- One third of the world's population is infected with Mycobacterium tuberculosis
- People infected with HIV are at much increased risk of developing active tuberculosis
- Short term preventive drug treatment given to people infected with HIV reduces the occurrence of active tuberculosis
- The benefit is greatest in people with latent infection, as shown by a positive skin test for tuberculosis, and this group also exhibits a survival benefit

Choice of drug regimen

Which drug regimen should be recommended? This review did not set out to answer this question.However, in the trial which tested three different regimens against placebo, isoniazid had the greatest effect,[12] although isoniazid and rifampicin combined and isoniazid, rifampicin, and pyrazinamide combined also reduced the incidence of tuberculosis. Halsey et al compared two regimens and reported similar protection conferred by twice weekly isoniazid given for 6 months and combined rifampicin and pyrazinamide given for 2 months.[14] Trials using combination treatment report higher rates of adverse drug reaction than do those using isoniazid alone. Adherence to preventive treatment was generally poor in these trials. Choice of regimen to implement in practice is likely to depend on anticipated adherence, cost, availability of drugs, concern over adverse drug reactions, and prevalence of drug resistance in the population. The strongest available evidence is for the use of isoniazid.

Although not reported as a problem in subjects who developed tuberculosis in these trials, widespread and unsupervised use of tuberculosis drugs is of concern, and monitoring for the development of drug resistance should take place. Adverse drug reactions were reported infrequently in these trials and although reassuring, monitoring of large numbers of subjects will be required to determine the incidence of infrequent but life threatening events such as hepatitis in association with isoniazid.

Preventive treatment and tuberculosis control

Although reduction in individual risk of tuberculosis is substantial, unless a large proportion of the affected population receives preventive treatment it seems unlikely that this intervention will substantially reduce disease transmission in countries with a high tuberculosis prevalence. The priority for tuberculosis control remains the early detection and treatment of active cases. Preventive treatment may be a useful intervention for individuals and for targeted groups such as factory workers, hospital staff, police, and the armed forces[17] who may have access to HIV testing, counselling, and ongoing care. These conclusions are in accord with current recommendations from the World Health Organisation and the International Union Against Tuberculosis and Lung Disease.[18] This policy, and future refinements to it, can now be based on a body of systematically reviewed data from relevant trials that provides accurate estimates of effect, and that is constantly updated.[19]

There remains a need to determine the long term impact of preventive treatment on tuberculosis and death, and the results of trials testing the efficacy of life long preventive treatment in adults infected with HIV are awaited. It will also be important to study the logistical barriers to implementing preventive treatment in different settings.[20]

This review is concurrently available on the infectious diseases module of the Cochrane Database of Systematic Reviews and will be updated as new data become available. We thank Dr Mark Hawken, who made original trial data available rapidly and courteously. Contributors: DW generated the idea for this review, developed the protocol, conducted the review, and wrote the paper; he will act as guarantor for the paper. SBS provided input on the protocol

development and interpretation of the review and commented on the manuscript. PG was coordinating editor for the review and oversaw its quality throughout, provided methodological support, and commented on the manuscript.
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Conflict of interest: None.

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Annex 2.6 Articles for review (Activity 2.2)

Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme

*Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees**

Summary

Background Patients with chronic heart failure (CHF) are at high risk of cardiovascular death and recurrent hospital admissions. We aimed to find out whether the use of an angiotensin-receptor blocker could reduce mortality and morbidity.

Methods In parallel, randomised, double-blind, controlled, clinical trials we compared candesartan with placebo in three distinct populations. We studied patients with left-ventricular ejection fraction (LVEF) 40% or less who were not receiving angiotensin-converting-enzyme inhibitors because of previous intolerance or who were currently receiving angiotensinconverting-enzyme inhibitors, and patients with LVEF higher than 40%. Overall, 7601 patients (7599 with data) were randomly assigned candesartan (n=3803, titrated to 32 mg once daily) or matching placebo (n=3796), and followed up for at least 2 years. The primary outcome of the overall programme was all-cause mortality, and for all the component trials was cardiovascular death or hospital admission for CHF. Analysis was by intention to treat.

Findings Median follow-up was 37·7 months. 886 (23%) patients in the candesartan and 945 (25%) in the placebo group died (unadjusted hazard ratio 0·91 [95% CI 0·83–1·00], p=0·055; covariate adjusted 0·90 [0·82–0·99], p=0·032), with fewer cardiovascular deaths (691 [18%] *vs* 769 [20%], unadjusted 0·88 [0·79–0·97], p=0·012; covariate adjusted 0·87 [0·78–0·96], p=0·006) and hospital admissions for CHF (757 [20%] *vs* 918 [24%], p<0·0001) in the candesartan group. There was no significant heterogeneity for candesartan results across the component trials. More patients discontinued candesartan than placebo because of concerns about renal function, hypotension, and hyperkalaemia.

Interpretation Candesartan was generally well tolerated and significantly reduced cardiovascular deaths and hospital admissions for heart failure. Ejection fraction or treatment at baseline did not alter these effects.

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Introduction

In patients with chronic heart failure (CHF) and reduced left-ventricular ejection fraction (LVEF), results of clinical randomised trials have shown the life-saving and symptomatic benefits of angiotensin-converting-enzyme inhibitors,[1–3] blockers,[4–7]and, in more selected patients, spironolactone.[8] These findings have led to widespread use of these treatments in appropriate populations.[9] The results have been translated into benefits in clinical practice, since in epidemiological studies and large registries substantial temporally related reductions have been seen in the ageadjusted mortality of patients with heart failure.[10–12] Despite these major successes, the prevalence of heart failure continues to increase, mainly as a consequence of ageing populations, many patients having hypertension, ischaemic heart disease, or both, the two main predisposing disorders for heart failure.[13–15] Indeed, heart failure is the most common reason for hospital admission in patients older than 65 years.[16,17] About 35–50% of patients with signs and symptoms attributed to heart failure do not have substantially reduced LVEF.[17] Irrespective of the cause or presence of left-ventricular dysfunction, once clinically recognised, patients with heart failure are at heightened risk for subsequent hospital admissions and death from cardiovascular causes.

The development of angiotensin II type 1 receptor blockers provides a pharmacologically distinct mechanism of inhibiting the renin-angiotensin-aldosterone system. Angiotensin-receptor blockers offer the potential to improve clinical outcomes for patients with heart failure beyond those seen with angiotensin-converting-enzyme inhibitors, as well as providing an alternative for patients with previous intolerance of angiotensin-converting-enzyme inhibitors.[18] The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme was specifically designed as three parallel, independent, integrated, randomised, double-blind, placebo-controlled, clinical trials comparing candesartan with placebo in three distinct but complementary populations

of patients with symptomatic heart failure.[19] Dependent on background use of angiotensin-converting-enzyme inhibitors or LVEF, patients were eligible for one of the three component trials. We designed each trial to find out whether the use of candesartan would reduce the risk of cardiovascular death or hospital admission for CHF management in the specific population. The overarching hypothesis of the CHARM programme prespecified that use of candesartan would reduce the risk of death from any cause in the broad spectrum of patients with heart failure. The population was appropriate to test for consistency of benefits in subgroups and potential safety issues.

Patients and methods

Patients

Eligible patients were women and men aged 18 years or older who had symptomatic heart failure (New York Heart Association class II–IV) for at least 4 weeks' duration. Major exclusion criteria included serum creatinine 265 mol/L or more, serum potassium 5·5 mmol/L or more, known bilateral renal artery stenosis, symptomatic hypotension, women of childbearing potential not using adequate contraception, critical aortic or mitral stenosis, myocardial infarction, stroke, or open-heart surgery in the previous 4 weeks, use of an angiotensin-receptor blocker in the previous 2 weeks, any non-cardiac disease judged likely to limit 2-year survival, and unwillingness to consent. Other exclusion criteria have been previously described.[19]

Eligible patients were enrolled into one of three trials, done concurrently, according to LVEF higher than 40% (CHARM-Preserved), 40% or lower and being treated with an angiotensin-converting-enzyme inhibitor (CHARM-Added), or 40% or lower and not being treated with an angiotensin-converting-enzyme inhibitor because of previous intolerance (CHARM-Alternative). All patients gave written informed consent before being enrolled. All sites received approval from local ethics committees for the conduct of each of the three component trials.

The component trials were all done at the same 618 sites in 26 countries, with use of uniform procedures, definitions, and forms, and one data coordinating centre, management, and leadership team. An independent data safety monitoring board was established to oversee the safety of patients enrolled in the trial and to monitor trial progress. This board had access to all data through an independent statistical centre. Predefined stopping rules for efficacy or safety concentrated on mortality from the overall trial programme. An independent clinical-event committee adjudicated all study endpoints.

Methods

Between March, 1999, and March, 2001, patients were randomly assigned, in a double-blind way, candesartan or matching placebo (figure 1) according to computergenerated assignment, stratified by site and component trial, and provided through a coordinating telephone centre. The assignment code was held at an independent centre and by the data safety monitoring board. The initial dose used could be 4 mg or 8 mg candesartan once daily or matching placebo, decided by the study physician.[19] Study-drug dose could be doubled, as tolerated, at a minimum of every 2 weeks, to the target dose of 32 mg once daily, with recommended monitoring of blood pressure and serum potassium and creatinine. Study medication could be increased or decreased in response to the patients' clinical status, and algorithms were provided as guidelines for management of hypotension or renal dysfunction. After the titration phase, visits were scheduled every 4 months, with a minimum planned duration of 2 years. Routine safety laboratory assessments were done in North American patients at baseline, 6 weeks, 14 months, and yearly thereafter. Use of conventional heart-failure treatments, such as blockers, diuretics, digitalis, spironolactone, and, if appropriate, angiotensin-converting-enzyme inhibitors, were allowed. After the results of the Heart Outcomes Prevention Evaluation trial[20] were available, physicians were permitted to use angiotensinconverting-enzyme inhibitors in CHARM-Preserved patients who had similar demographic features. Patients were free to discontinue their participation in the study at any time. Discontinuations because of patients' preference or physicians' decision were recorded and these patients were followed up for outcomes if possible, according to the intention-to-treat principle.

The primary outcome of the overall programme was allcause death. The outcomes in the three component trials were: cardiovascular death or unplanned admission to hospital for the management of worsening CHF (primary outcome); cardiovascular death, admission to hospital for CHF, or non-fatal myocardial infarction; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, or non-fatal stroke; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation; death (any cause) or admission to hospital for CHF; and development of new diabetes.

We classified all deaths as cardiovascular unless an unequivocal non-cardiovascular cause was established. A CHF hospital admission was defined as admission to hospital necessitated by heart failure and primarily for its treatment or when heart failure became a major component of the patient's hosiptal admission. A patient admitted for this reason had to show signs and symptoms of worsening heart failure and require treatment with intravenous diuretics. Evidence of worsening heart failure had to include at least one of the following items: increasing dyspnoea on exertion, orthopnoea, nocturnal dyspnoea, pulmonary oedema, increasing peripheral oedema, increasing fatigue or decreasing exercise tolerance, renal hypoperfusion (ie, worsening renal function), raised jugular venous pressure, and radiological signs of CHF.

A diagnosis of myocardial infarction was made if the following conditions were met: creatine kinase or creatine kinase-MB more than twice the upper limit of normal, or troponin I or T more than twice the upper limit of normal if neither creatine kinase or creatine kinase-MB were available; or three times the upper limit of normal for the same markers within 24 h of percutaneous transluminal coronary angioplasty; or five times the upper limit of normal for the same markers within 24 h of coronary artery bypass grafting surgery. In addition to these marker criteria, a patient had to have experienced electrocardiographic changes in two or more contiguous leads showing new Q waves (or R waves in V1 or V2), leftbundle-branch block, or ischaemic ST-T wave changes, or typical clinical presentation consistent with myocardial infarction defined as one of the following: cardiac ischaemic type pain lasting more than 20 min, pulmonary oedema, or cardiogenic shock not otherwise explained.

Statistical methods

Each component trial independently estimated its respective sample size based on the anticipated event rate for the combined outcome of cardiovascular death or admission to hospital for CHF. We designed the overall

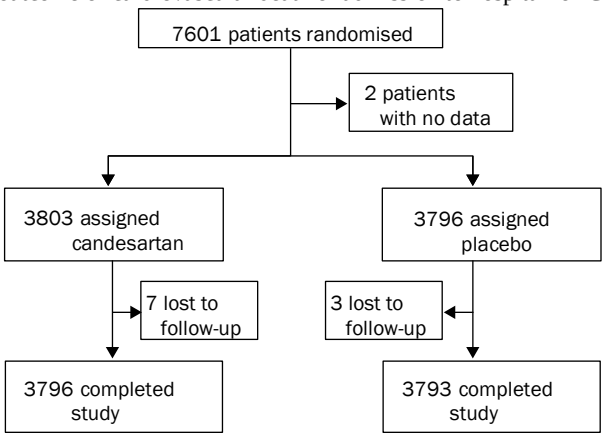

Figure 1: Trial profile

	Candesartan (n=3803)	Placebo (n=3796)
Mean (SD) age (years)	65·9 (11·0)	66·0 (11·1)
75 years	852 (22·4%)	884 (23·3%)
Men/women	2617 (68·8%)/ 1186 (31·2%)	2582 (68·0%)/ 1214 (32·0%)
Ethnic origin		
European	3412 (89·7%)	3458 (91·1%)
Black	162 (4·3%)	164 (4·3%)
Other	229 (6·0%)	174 (4·6%)
Heart-disease risk factors		
NYHA class		
II	1730 (45·5%)	1686 (44·4%)
III	1977 (52·0%)	2008 (52·9%)
IV	96 (2·5%)	102 (2·7%)
Mean (SD) LVEF (%)	38·8 (14·9)	38·8 (14·9)
<30	1073 (28·2%)	1045 (27·5%)
30–39	1083 (28·5%)	1123 (29·6%)
40–49	667 (17·5%)	655 (17·3%)
50	980 (25·8%	973 (25·6%)
Mean (SD) heart rate (beats/min)	73·0 (13·3)	72·8 (12·8)
Mean (SD) blood pressure (mm Hg)		
Systolic	130·6 (19·3)	131·1 (19·0)
Diastolic	76·6 (10·9)	76·7 (10·6)
Mean (SD) body-mass index (kg/m²)	28·3 (5·6)	28·2 (5·3)
Medical history		
Hospital admission for CHF	2725 (71·7%)	2701 (71·2%)
Myocardial infarction	2024 (53·2%)	1980 (52·2%)
Current angina	872 (22·9%)	936 (24·7%)
Stroke	333 (8·8%)	330 (8·7%)
Diabetes mellitus	1085 (28·6%)	1075 (28·3%)
Hypertension	2093 (55·0)	2093 (55·1%)
Atrial fibrillation	1039 (27·3%)	1044 (27·5%)
Pacemaker	313 (8·2%)	324 (8·5%)
Current smoker	565 (14·9%)	549 (14·5%)
PCI	575 (15·1%)	653 (17·2%)
CABG	921 (24·2%)	870 (22·9%)
Implantable cardioverter defibrillator	98 (2·6%)	93 (2·4%)
Previous cancer	270 (7·1%)	243 (6·4%)
Patients' characteristics		
Medical treatment		
ACE inhibitor	1573 (41·4%)	1552 (40·9%)
blocker	2102 (55·3%)	2101 (55·3%)
Diuretic	3150 (82·8%)	3136 (82·6%)
Spironolactone	643 (16·9%)	629 (16·6%)
Digoxin/digitalis glycoside	1622 (42·7%)	1632 (43·0%)
Calcium antagonist	768 (20·2%)	774 (20·4%)
Other vasodilators	1437 (37·8%)	1527 (40·2%)
Oral anticoagulants	1182 (31·1%)	1156 (30·5%)
Antiarhythmic agents	443 (11·6%)	450 (11·9%)
Aspirin	2105 (55·4%)	2141 (56·4%)
Other antiplatelet agent	181 (4·8%)	175 (4·6%)
Lipid-lowering drug	1578 (41·5%)	1575 (41·5%)

NYHA=New York Heart Association. ACE=angiotensin-converting enzyme. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. All baseline variables listed, except ethnic origin, heart failure cause, and baseline spironolactone treatment, used as covariates. Table 1: Baseline characteristics of patients

study to address the question of all-cause mortality in all randomised patients, with its sample size being based on the sum of the three trials. We estimated an annual overall mortality in the placebo group of 8% and, on that basis, the programme of investigation had more than 85% power to detect around a 14% reduction in mortality at a significance level of 0·05, based on the logrank test. All analyses were done by intention to treat, and p values were two-sided. Cardiovascular death, hospital admission for heart failure, or non-fatal myocardial infarction, for the primary and secondary analyses were based on the adjudicated approved events. The hierarchical secondary analyses also included the non-adjudicated outcomes of non-fatal stroke and coronary revascularisation procedures. Investigator-reported outcomes and new onset of diabetes mellitus were prespecified additional outcomes. All time-to-event variables were analysed with the logrank test and displayed on Kaplan-Meier plots according to treatment. We estimated the hazard ratios and 95% CI comparing treatments, stratified by trial, with a stratified logrank test. In addition, a covariate-adjusted Cox's regression model was fitted with the prespecified baseline covariates shown in table 1 to adjust the hazard ratio for other factors that might affect prognosis. Prespecified subgroup analyses were done, each using a test for heterogeneity to assess for possible interactions between treatment and baseline variables. We combined data from the two studies of patients with LVEF 40% or less because this subgroup was prespecified as clinically important. We grouped major non-cardiovascular events by specific cause and for safety analyses. We compared the rates and proportions of patients who discontinued blinded study medication overall, as well as for specific reasons such as hypotension, increased creatinine, and hyperkalaemia for safety and tolerability assessments.

Role of the funding source

The sponsor of the study managed the data, and its representatives were involved in the data analysis and data interpretation. All final data analyses were done by the
sponsor and verified independently by the statistical centre at London School of Hygiene and Tropical Medicine, London, UK.

Results

7601 patients were randomised, although no data were available on two patients incorrectly assigned randomisation numbers and, therefore, the results are based on 7599 patients (3803 candesartan, 3796 placebo, figure 1). The programme was completed as planned with follow-up concluding on March 31, 2003, 2 years after the last patient was randomised. The median duration of follow-up was 37·7 months and the vital status of all but ten (0·1%) patients was ascertained at study closure. The baseline characteristics of the placebo and candesartan groups are shown in table 1.[21]

886 (23%) in the candesartan group and 945 (25%) in the placebo group died from any cause (unadjusted hazard ratio 0·91 [95% CI 0·83–1·00)], p=0·055; covariate adjusted 0·90 [0·82–0·99], p=0·032, figure 2). Annual mortality rates (events per 100 years of follow-up) were 8·1% and 8·8%, respectively. This lower mortality in the candesartan group was attributable to fewer cardiovascular deaths: 691 (18%) in the candesartan compared with 769 (20%) in the placebo group (unadjusted 0·88 [0·79–0·97], p=0·012; covariate adjusted 0·87 [0·78–0·96], p=0·006, figure 2). This treatment difference in cardiovascular death was most striking in the first year but was maintained without additional divergence in subsequent years.

The reductions in death, particularly cardiovascular death, were seen among patients with LVEF of 40% or less, with significant reductions in all-cause mortality (0·88 [0·79–0·98], p=0·018) and cardiovascular deaths (0·84 [0·75–0·95], p=0·005). There was, however, no significant heterogeneity across the three trials in the impact of candesartan on all-cause mortality (figure 3) or cardiovascular deaths or hospital admission for CHF (interaction test, p=0·37 and p=0·43, respectively).

There were slightly more non-cardiovascular deaths in the candesartan group than in the placebo group (195 [5%] *vs* 176 [5%]; p=0·45), which was due to a difference in cancer deaths (86 [2·3%] *vs* 59 [1·6%], p=0·038). The incidence of non-fatal neoplasms detected during the programme was, however, similar in the two treatment groups (185 [5·1%] *vs* 194 [4·6%], p=0·49).

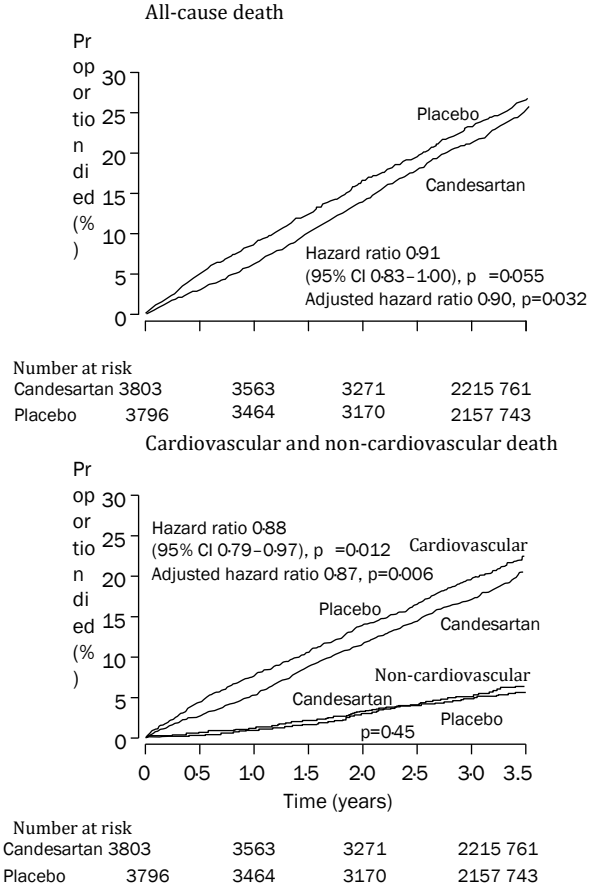

Figure 2: Kaplan-Meier curves of all-cause death and cardiovascular or non-cardiovascular deaths

Overall, time to cardiovascular death or hospital admission for CHF, the primary outcome for each of the three component trials, was reduced by 16% (candesartan 30%, placebo 35%, adjusted 0·84 [0·77–0·91], p<0·0001; covariate adjusted 0·82 [0·75–0·88], p<0·0001, figure 4). This reduction in risk with candesartan was consistent across all trials (heterogeneity p=0·33, figure 3).[22–24] Risk of cardiovascular death and risk of first hospital admission for CHF were each significantly reduced: 757 (20%) of candesartan

patients compared with 918 (24%) placebo patients had at least one adjudicated hospital admission for CHF (p<0·0001). Moreover, there were 1454 investigator-reported hospital admissions for CHF as the primary cause in the candesartan patients compared with 2010 in the placebo group (p<0·0001). Two or more hospital admissions for heart failure were reported in 339 (9%) candesartan and 456 (12%) placebo patients (p<0·0001). This risk reduction in time to cardiovascular death and non-fatal cardiovascular outcomes by

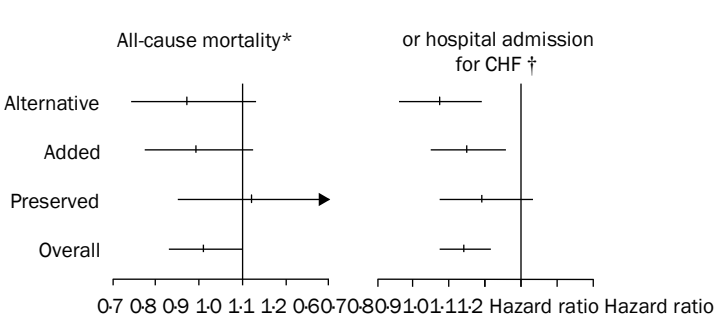

Figure 3: Effects of candesartan on all-cause mortality, cardiovascular death, or hospital admission for CHF *p for heterogeneity 0·37. †p for heterogeneity 0·33.

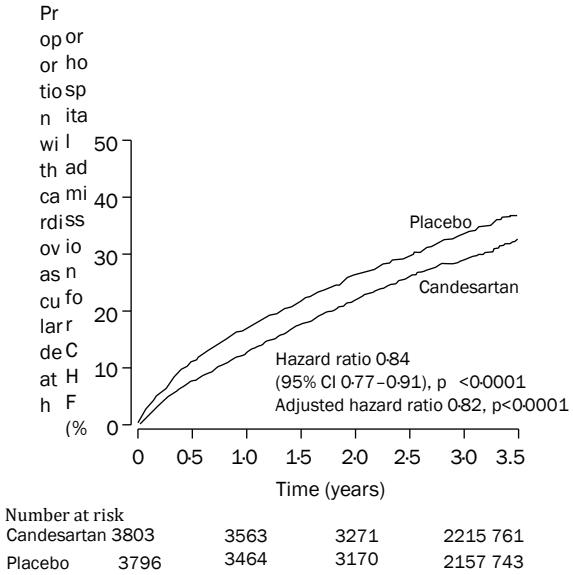

Figure 4: Effect of candesartan on cardiovascular mortality or hospital admission for CHF

candesartan was maintained as the composite outcome of cardiovascular death or hospital admission for CHF was expanded in a prespecified stepwise way to include nonfatal myocardial infarction, non-fatal stroke, and coronary revascularisation procedures (table 2). The total number of patients with myocardial infarction was: candesartan 176, placebo 190 (p=0·33); stroke: candesartan 141, placebo 146 (p=0·63); and coronary revascularisation procedure: candesartan 236, placebo 241 (p=0·62). In the candesartan group, 2374 patients had 6690 hospital admissions for any reason compared with 2423 placebo patients who had 7178 admissions (p=0·2 for patients and p=0·015 for admissions).

Overall, 1398 (37%) candesartan and 1541 (41%) placebo patients died (any cause) or were admitted for CHF (0·86 [0·80–0·93], p<0·0001). In patients without a prestudy diagnosis of diabetes, the number of patients in the candesartan group who during the programme were newly diagnosed as having diabetes was significantly lower than that in the placebo group: candesartan 163 (6%) of 2715 and placebo 202 (7%) of 2721 (0·78 [0·64–0·96], p=0·020; test for heterogeneity between trials, p=0·163).

The reduction in risk of cardiovascular death or hospital admission for heart failure with candesartan was similar in men and women (figure 5). Similarly, the 1736 patients aged 75 years or older showed as great a benefit with candesartan as did younger patients. Particularly noteworthy was the similar effectiveness of candesartan in patients with LVEF higher or lower than 40% (figure 5). The relative reductions in risk were similar across New York Heart Association classes and among patients with or without a history of diabetes at baseline (figure 5). The beneficial effect of candesartan was consistent irrespective of baseline concomitant medications used. Specifically, similar benefits were noted whether or not ACE inhibitors, blockers, spironolactone, any diuretic, digitalis glycoside, aspirin, or lipid-lowering drugs were used at baseline (figure 5).

The initial dose of study medication was 4 mg in 80% and 8 mg in 20% of patients. At the 6-month visit, study medication had been discontinued in 404 (11%) of the candesartan patients and 265 (7%) of placebo patients (p<0·0001). Of those taking study medication at that time, 2025 (63%) of candesartan patients were at the target dose (32 mg once daily) compared with 2489 (75%) of the placebo group. At 6 months, the mean daily doses were 24 mg and 27 mg, respectively, and were similar at subsequent visits. By the end of the studies, 660 (23%) of candesartan survivors and 529 (19%) of placebo

	Candesartan	Placebo	Unadjusted hazard p	Adjusted hazard	p (n=3803)	(n=3796)	ratio (95% CI) ratio (95% CI)*
Cardiovascular death or hospital admissions for CHF	1150 (30·2%)	1310 (34·5%)	0·84 (0·77–0·91)	<0·0001	0·82 (0·75–0·88)		<0·0001
Cardiovascular death	691 (18·2%)	769 (20·3%)	0·88 (0·79–0·97)	0·012	0·87 (0·78–0·96)		0·006
Hospital admission for CHF	757 (19·9%)	918 (24·2%)	0·79 (0·72–0·87)	<0·0001	0·77 (0·70–0·84)		<0·0001
Cardiovascular death, hospital admission for CHF, MI	1213 (31·9%)	1369 (36·1%)	0·84 (0·78–0·91)	<0·0001	0·82 (0·76–0·89)		<0·0001
Cardiovascular death, hospital admission for CHF, MI, stroke	1269 (33·4%)	1420 (37·4%)	0·85 (0·79–0·92)	<0·0001	0·83 (0·77–0·90)		<0·0001
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	1404 (36·9%)	1549 (40·8%)	0·86 (0·80–0·93)	<0·0001	0·85 (0·79–0·92)		<0·0001

MI=myocardial infarction. *Covariate adjusted model for variables shown in table 1.

Table 2: Secondary outcomes hierarchically ordered

survivors were no longer taking study medication for any reason (p=0·0001). Permanent discontinuations for adverse events or abnormal laboratory values were more frequent with candesartan (table 3). Angioedema was reported in five (0·13%) candesartanassigned patients and three (0·08%) patients in the placebo group.

Surveillance blood safety analyses were done in 2743 North American patients. Between baseline and 6 weeks, serum creatinine changed slightly in the two treatment groups (8 mol/L increase in the candesartan group and 1 mol/L decrease in the placebo group). Creatinine doubled in 82 (6%) of 1263 candesartan patients and 47 (4%) of 1279 of placebo patients with surveillance laboratory assessments (p=0·002). At 6 weeks, there was a 0·14 mmol/L increase in serum potassium (p<0·0001) in the candesartan group with no overall change in the placebo group. A potassium concentration of 6·0 mmol/L or higher was seen in 31 (2%) of 1294 candesartan and 15 (1%) of 1310 placebo patients (p=0·017). No other unexpected or clinically important changes in laboratory values were noted. By 6 months, blood pressure was lowered from baseline by 5·2 mm Hg systolic and 3·0 mm Hg diastolic more in the candesartan group than in the placebo (p<0·001 for both), with more lowering of blood pressure in CHARM-Preserved (test for heterogeneity for systolic p=0·025, for diastolic p=0·021).

Discussion

Our results show that treatment of a broad spectrum of patients with symptomatic heart failure with candesartan resulted in a reduction in deaths, albeit of borderline significance, notably because of a significant 12% reduction in cardiovascular deaths. In the overall CHARM programme, the risk of death and, particularly, death attributed to cardiovascular causes was

Age Candesartan Placebo Test for interaction

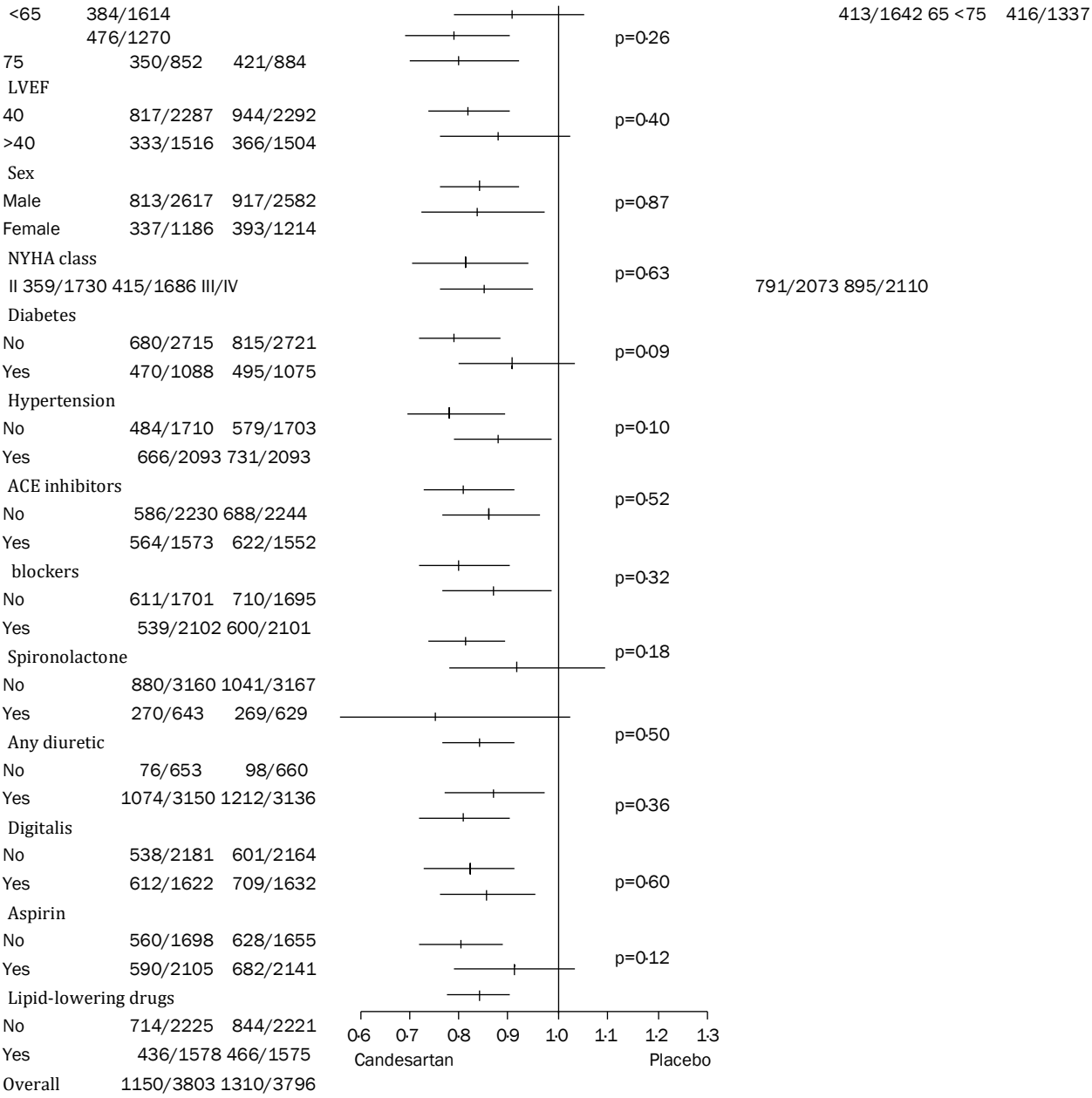

Figure 5: Overall effect of candesartan on cardiovascular death or first admission for CHF in prespecified subgroups

Point estimates of hazard ratios given with 95% CI. p values are for heterogeneity.

	Candesartan (n=3803)	Placebo (n=3796)	p
Cause of discontinuation			
Hypotension	132 (3·5%)	66 (1·7%)	<0·0001
Increase in serum creatinine	234 (6·2%)	115 (3·0)	<0·0001
Hyperkalaemia	85 (2·2%)	21 (0·6%)	<0·0001
Any adverse event or laboratory abnormality	797 (21·0%)	633 (16·7)	<0·0001

Table 3: Permanent study-drug discontinuations for adverse events

strongly affected by left-ventricular systolic function. The annual cardiovascular death rate among the placebo group who had reduced LVEF was around 9%[22,23] and was only 4% in the placebo group of CHARM-Preserved.[24] However, the annual non-cardiovascular death rate of about 2% per year in the placebo group was similar in all component trials. In the patients with LVEF higher than 40%, who had a substantially lower risk of dying of a cardiovascular cause than did patients with lower LVEF, candesartan did not seem to alter survival. However, the absence of heterogeneity in treatment effect across trials and by LVEF, and the reduction in hospital admissions for heart failure in this lower-risk group, does provide an indication that worthwhile clinical benefits were derived from candesartan.

Our prespecified analysis of the mortality results from the two low LVEF trials shows a clear prolongation in survival with candesartan, a significant reduction in all deaths, and a 16% lower rate of cardiovascular death. This reduction in cardiovascular deaths was complemented by significant reductions in hospital admissions for the management of heart failure in all component trials.

The concept that inhibition of the renin-angiotensin system by blockade at the angiotensin II type 1 receptor can result in more complete inhibition of the adverse cardiovascular effects of angiotensin II while leaving unopposed other potentially desirable actions modulated by different angiotensin II receptors has stimulated much interest and clinical investigation. Angiotensin-receptor blockers effectively reduce important non-fatal clinical events in hypertensive patients who have diabetes and nephropathy,[25,26] hypertensive patients with electrocardiographic evidence of left-ventricular hypertrophy,[27] elderly patients with hypertension,[28] and those with symptomatic heart failure and depressed ejection fraction.[29] However, a survival advantage produced by angiotensin-receptor blockers in patients with heart failure and reduced LVEF has not been clearly shown,[29,30] nor in any other high-risk population studied. We show that candesartan offers survival benefits in patients with CHF and reduced LVEF. However, we cannot tell to what extent this improvement in survival was related to the 32 mg daily target dose of candesartan or other potentially distinctive pharmacological properties.[31]

In patients with heart failure and reduced LVEF, it has been suggested that additional survival benefits could not be achieved with angiotensin-receptor blockers among those already taking proven effective treatments, including angiotensin-converting-enzyme inhibitors and blockers.[32] Our two cohorts of patients with symptomatic heart failure (LVEF 40%) prespecified by use of angiotensin-converting-enzyme inhibitor and with substantial -blocker use, is particularly well suited to address this question. The reductions in cardiovascular death with candesartan were similar in patients taking angiotensin-converting-enzyme inhibitors and not taking them because of intolerance. Similarly, the similarity of clinical-outcome benefits irrespective of blocker use suggests that candesartan offers additive benefits and complementary mechanisms to these other proven treatments.

The primary outcome of all the component CHARM trials, time to cardiovascular death or adjudicated hospital admission for CHF, was consistently reduced in symptomatic heart-failure patients. This finding, based on more than 20000 patient-years and more than 2450 events, is robust, and suggests that patients who have symptomatic heart failure will derive important clinical benefits from candesartan. The absence of heterogeneity in results underscores that this benefit was achieved across a broad spectrum of patients. Subgroup analyses must be interpreted cautiously since the most rigorous test of the study hypothesis is derived from the entire population, in which consistency of this benefit was seen. Similar reductions in mortality and morbidity outcomes with the use of candesartan were obtained in women and men, those with and without diabetes, and importantly, across age-groups, a substantial number of patients being older than 75 years. The beneficial effects of candesartan in the CHARM programme were not altered by baseline use of blockers, spironolactone, digoxin, aspirin, and lipid-lowering treatments. This added efficacy on top of blockers is particularly noteworthy, since 55% of CHARM patients at baseline were receiving these drugs, and a previous subgroup analysis from the Valsartan Heart Failure Trial[29] suggested less benefit of an angiotensin-receptor blocker in patients already receiving blockers.

The use of candesartan in patients with symptomatic heart failure did not significantly reduce the risk of myocardial infarction, stroke, or use of coronary revascularisation procedures. However, the significant benefits of candesartan treatment were maintained when these non-fatal cardiovascular events were incorporated with admission to hospital for heart failure and cardiovascular death in a prespecified analysis of time to first event. Lowering of blood pressure was more pronounced in CHARM-Preserved than in the other component trials and did not seem to be related to improved clinical outcome. The frequency of new diabetes was lower in the candesartan group than in the placebo group, which is an effect that has been seen in other large populations treated with inhibitors of angiotensin-converting enzyme[33] and angiotensin-receptor blockers.[27,28]

Candesartan was generally well tolerated but was associated with a greater occurrence of discontinuation of study medication than was placebo because of hypotension, hyperkalaemia, and an increase in serum creatinine, underscoring the need to monitor patients. Although more cancer deaths occurred in the candesartan group, we attributed this imbalance to the play of chance, since the investigator-reported rate of non-fatal neoplasms did not differ between treatment groups. Moreover, including CHARM together with the entire previous candesartan placebo-controlled trial experience (AstraZeneca, data on file), there were 523 (144 fatal) investigator-reported neoplasms, including cancers, during 20692 patient-years of exposure to candesartan compared with 491 (125 fatal) in 20135 patient-years with placebo (p=0·6 and p=0·4, respectively). No consistent differences in fatal or non-fatal neoplasms at different sites have been noted between candesartan and placebo.

Our findings show that candesartan, given in titrated doses as tolerated, can prolong survival, particularly in patients with LVEF of 40% or less, and provide incremental clinical benefits across the broad spectrum of patients with symptomatic heart failure, including reductions in hospital admissions for heart failure and prevention of diabetes. This effect is consistent for the combined cardiovascular mortality and morbidity outcome, irrespective of other effective concomitant treatments, ejection fraction, age, and sex. The clinical effectiveness we report for candesartan in the treatment of chronic heart failure offers the opportunity to further reduce cardiovascular mortality and morbidity in this expanding segment of our ageing population.

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Conflict of interest statement

M A Pfeffer, K Swedberg, C B Granger, J J V McMurray, and S Yusuf have served as consultants to or received research grants from AstraZeneca and other major cardiovascular pharmaceutical companies. J Östergren served as consultant and received research grants from AstraZeneca. P Held, E L Michelson, and B Olofsson are employees of AstraZeneca.

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Annex 2.7. Answers to Activity 2. 1 (based on systematic review by D. Wilkinson et al.)

Clear review question stated (question type*, population, intervention and outcome)?	Yes – Question type: Prevention; therapy (preventive) Population: Adults infected with HIV Intervention: preventive treatment for tuberculosis Outcomes: 1. Frequency of TB, 2. Overall mortality
Included study designs stated?	Yes – Randomized controlled trials only (see Subjects and Methods, Criteria for selecting studies for review)
— Criteria used to assess the quality of studies	(See Review procedure): "The quality of each trial was graded using predefined criteria, assessing method of allocation sequence generation, allocation concealment, inclusion of all randomised participants, follow up of subjects, and analysis by intention to treat."
— Study characteristics documented for included studies?	Yes (see Table 1)
Inclusion/exclusion criteria stated?	Yes – (see under Criteria for selecting studies for review:) "We included only randomised controlled trials that compared drug regimens aimed at preventing tuberculosis with placebo. Trials were considered irrespective of setting or target group, and we included all different drug regimens tested. Preventive treatment was defined as tuberculosis chemotherapy given to people who have a particular risk of developing tuberculosis. Particular risk refers to ..." (etc.) (Review procedure): "Trials considered for inclusion were examined to determine completeness of reporting." ... "Authors of incomplete or abstracted trials were contacted for further details." (see Results): "Exclusion criteria were similar in all trials and included past history of tuberculosis, current tuberculosis, pregnancy, abnormal liver enzymes, and serious intercurrent illness."
Literature search strategy recorded?	Yes – (see Search strategy) "We searched Medline using the search terms HIV, tuberculosis, preventive therapy, and chemoprophylaxis. We also searched the Cochrane Controlled Trials Register, the most comprehensive source of controlled trials (disk issue 1, 1998). In addition, we searched references of all retrieved articles and contacted relevant researchers to ensure that all completed trials had been identified. "
Data abstracted in a manner consistent with the review question?	Yes – see definition of outcomes given under Outcome measures. The presence of active TB was defined in several ways (microbiologically, histologically, clinically) Results were stratified by PPD status where possible
Reproducible and bias-free process of — identifying studies? — including studies? — abstracting data?	Yes — Comprehensive search strategy — Clear inclusion criteria appropriate to the type of review question; efforts were made to obtain data for studies where results were incomplete — Clearly and appropriately defined outcomes, one researcher abstracted data, another checked collated data (see Review procedure) See paragraphs on possible biases. Information on contributors and funding included; no declared conflicts of interest (last paragraphs before references)

Relevant, justifiable bottom line?	Yes – TB infection and mortality are relevant endpoints; stratification by PPD status allowed conclusions for subgroups; relatively brief follow-up times are discussed as a limitation (see Discussion)
Meta-analysis for different outcomes used (appropriately)?	Yes – Results were analyzed with approved methodology – relative risk, 95% confidence intervals, weighting of individual trials according to sample size and trial quality (see table)
Up-to-date?	Yes – study accepted for publication in July 1998; Publications of that year are included in the list of references

Annex 2.8: Answers to exercise 2. 2 on Critical review

Candesartan reduced mortality and hospital admissions in chronic heart failure

Bertram Pitt

Evid. Based Med. 2004;9;44-45 doi:10.1136/ebm.9.2.44

Candesartan reduced mortality and hospital admissions in chronic heart failure

Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.

Clinical impact ratings GP/FP/Primary care wwwwwwq IM/Ambulatory care wwwwwwq Cardiology wwwwwwq

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Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772–6. Clinical impact ratings GP/FP/Primary care wwwwwwq IM/Ambulatory care wwwwwqq Cardiology wwwwwwq

Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet 2003;362:777–81.

Clinical impact ratings GP/FP/Primary care wwwwqqq IM/Ambulatory care wwwwwqq Cardiology wwwwwww

Q In patients with chronic heart failure (CHF), does the angiotensin-receptor blocker (ARB) candesartan reduce death and hospital admissions?

METHODS

Design: 3-component randomised, placebo controlled trial (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity [CHARM] study).

Allocation: concealed.*

Blinding: blinded (clinicians, patients, data collectors, outcome assessors, monitoring committee, manuscript writers, and data analysts).*

Follow up period: median 37.7 months.

Setting: 618 centres in 26 countries.

Patients: 7601 patients who were >18 years of age and had symptomatic CHF (New York Heart Association class II–IV) for >4 weeks. Major exclusion criteria included serum creatinine >265 mmol/l; serum potassium >5.5 mmol/l; bilateral renal artery stenosis; symptomatic hypotension; critical aortic or mitral stenosis; myocardial infarction, stroke, or open heart surgery in the previous 4 weeks; use of an ARB in the previous 2 weeks; other serious disease likely to limit 2 year survival; and potential for pregnancy. Patients were enrolled in 1 of 3 component trials: CHARM-Added involved patients with left ventricular ejection fraction (LVEF) (40% who were being treated with an angiotensin converting enzyme (ACE) inhibitor for >30 days (n = 2548); CHARM-Alternative involved patients with LVEF (40% who were intolerant of ACE inhibitors (n = 2028); and CHARM-Preserved involved patients with LVEF .40% (n = 3023). CHARM-Overall involved all patients.

For correspondence: Professor C H A R M-Overall: M A Pfeffer, Brigham and Women's Hospital, Boston, MA, USA. mpfeffer@rics.bwh.harvard.edu

For correspondence: Professor C H A R M-Added: J McMurray, Western Infirmary, Glasgow, UK. j.mcmurray@bio.gla.ac.uk

For correspondence: Dr C H A R M-Alternative: C B Granger, Duke University Medical Center, Durham, NC, USA. grang001@mc.duke.edu

For correspondence: Professor C H A R M-Preserved: S Yusuf, McMaster University, Hamilton, Ontario, Canada. yusufs@mcmaster.ca Source of funding: AstraZeneca R&D. www.evidence-basedmedicine.com

Intervention: stratified by site and component trial and allocated to candesartan, 4 or 8 mg once daily, doubled every 2 weeks to a target dose of 32 mg once daily from 6 weeks onwards (n = 3803) or placebo (n = 3796).

Outcomes: all cause mortality (CHARM-Overall) and a composite outcome of cardiovascular death or hospital admission for worsening CHF in the 3 component trials. Secondary outcomes included doubling of creatinine concentrations and potassium concentration >6.0 mmol/l.

Patient follow up: 7599 patients (mean age 66 y, 68% men) were included in the analysis; 7589 patients completed the study.

*See glossary.

MAIN RESULTS

Analysis was by intention to treat. Overall, all cause mortality was reduced more with candesartan than with placebo (table), mainly because of fewer cardiovascular deaths (18% v 20%, adjusted hazard ratio 0.87, 95% CI 0.78 to 0.96). Fewer patients who received candesartan had the composite outcome of cardiovascular death or hospital admission for CHF than did patients who received placebo in the CHARM-Added and CHARM-Alternative component trials (table). In CHARM-Preserved, the reduction in the composite outcome with candesartan reached borderline statistical significance (table). The rates of doubling creatinine concentration for the candesartan and placebo groups were 6% v 4% (p=0.002) (CHARM-Overall), 7% v 6% (p=0.5) (CHARM-Added), 5.5% v 1.6% (p=0.015) (CHARM-Alternative), and 6% v 3%, (p=0.007) (CHARM-Preserved). The rates for potassium concentration >6.0 mmol/l for the candesartan and placebo groups were 2% v 1% (p=0.017) (CHARM-Overall), 3% v 1% (p=0.089) (CHARMAdded), 3% v 1.3% (p=0.26) (CHARM-Alternative), and 2% v 1% (p=0.32) (CHARM-Preserved).

CONCLUSIONS

In patients with chronic heart failure (CHF), the angiotensin receptor blocker candesartan reduced mortality (particularly cardiovascular) and hospital admissions for worsening CHF. Patients with reduced left ventricular ejection fraction with or without baseline angiotensin converting enzyme inhibitor treatment showed the most benefit.

Abstract and commentary also appear in ACP Journal Club.

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Commentary

The CHARM study extends our knowledge of the role of ARBs in patients with CHF.

Least surprising but still important was the finding in the CHARMAlternative study that candesartan resulted in a significant reduction in cardiovascular mortality and hospital admission for heart failure. The Valsartan Heart Failure Trial (ValHeFT) reached a similar conclusion,[1] and valsartan is indicated in patients with heart failure caused by systolic left ventricular dysfunction who are not taking an ACE inhibitor. However, the result of ValHeFT was determined in a retrospective analysis and included a relatively small number of patients and events. The CHARM-Alternative study, on the other hand, was prospective and adequately powered with a significant number of events.

It is likely that ARBs used at the appropriate dose, such as valsartan 160 mg twice daily or candesartan 32 mg daily, are equivalent to target doses of an ACE inhibitor, such as enalapril 10 mg twice daily. However, the therapy of choice in patients with CHF caused by systolic left ventricular dysfunction will probably remain an ACE inhibitor because of the relatively large number of patients in whom these agents have been studied and their reasonable cost.

The CHARM-Added trial is also important because it suggests that an ARB should be added to an ACE inhibitor and a b blocker in patients with mild to moderate CHF caused by systolic left ventricular dysfunction. Whereas the reduction in cardiovascular mortality in the CHARM-Added trial was moderate, the reduction in the combined endpoint of cardiovascular mortality and hospital admission for heart failure is both clinically and statistically significant. ValHeFT suggested that in a patient with CHF already treated with both an ACE inhibitor and a b blocker, adding an ARB was associated with an increased risk of death. The CHARM-Added results, however, suggest that the ValHeFT results in this particular subset were due to chance.

Somewhat less clear is the explanation for the discrepancy between ValHeFT and CHARM on cardiovascular mortality. In ValHeFT, valsartan had no effect on cardiovascular mortality and its significant benefit on the combined endpoint of cardiovascular mortality and hospital admission for heart failure was entirely the result of a reduction in hospital admissions for heart failure. In the CHARM-Added study, there was a reduction in both cardiovascular mortality and hospital admissions for heart failure. Whether this disparity reflects a difference in the effectiveness of valsartan and candesartan, their relative dosing strategy, or other factors remains to be determined. A further study of an ARB in this situation would therefore be ethical and useful.

In patients with severe heart failure, an aldosterone blocker might be the preferred agent to add to an ACE inhibitor and a b blocker rather than an ARB based on the results of the Randomized Aldactone Evaluation Study (RALES).[2] However, in RALES only a relatively small proportion of patients were receiving both an ACE inhibitor and a b blocker. Direct comparative studies of an ARB and an aldosterone blocker when added to an ACE inhibitor and a b blocker in patients with CHF caused by systolic left ventricular dysfunction are needed.

In patients with CHF and preserved systolic function (CHARMPreserved), candesartan was shown to be of only marginal benefit. Further studies are clearly required to determine the optimal strategy to reduce cardiovascular events in this important subset of patients whose incidence is increasing because of aging and increasing incidence of hypertension and diabetes mellitus.

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Ann Arbor, Michigan, USA

1 Cohn JN, Tognoni G. A randomized trial of angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667–75.
2 Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–17.

Candesartan v placebo for chronic heart failure (CHF) at median 37.7 months*

Trial	Outcomes	Candesartan	Placebo	Unadjusted HR (95% CI)	Adjusted analysis		
					HR (CI)	RRR (CI)	NNT (CI)
Overall	All cause mortality	23%	25%	0.91 (0.83 to 1.00)	0.90 (0.82 to 0.99)	8.8% (0.9 to 16)	46 (26 to 463)
CHARM-Added	Composite	38%	42%	0.85 (0.75 to 0.96)	0.85 (0.75 to 0.96)	12% (3 to 20)	21 (12 to 79)
CHARM-Alternative	Composite	33%	40%	0.77 (0.67 to 0.89)	0.70 (0.60 to 0.81)	25% (15 to 34)	11 (8 to 17)
CHARM-Preserved	Composite	22%	24%	0.89 (0.77 to 1.03)	0.86 (0.74 to 1.00)	12% (0 to 23)	Borderline significance

*Composite endpoint = cardiovascular death or hospital admission for worsening CHF; CHARM = Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity; HR = hazard ratio. Other abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article using Cox proportional hazards model. Adjusted for baseline covariates, including patients' characteristics, heart disease risk factors, medical history, and medical treatment.

www.evidence-basedmedicine.com

Annex 2.9 Sequential process for developing guidelines

First steps	
1. Establishing the process—	For example, prioritizing problems, selecting a panel, declaring conflicts of interest, and agreeing on group processes
Preparatory steps	
2. Systematic review—	The first step is to identify and critically appraise or prepare systematic reviews of the best available evidence for all important outcomes
3. Prepare evidence profile for important outcomes--	Profiles are needed for each subpopulation or risk group, based on the results of systematic review, and should include a quality assessment and a summary of findings
Grading quality of evidence and strength of recommendations	
4. Quality of evidence for each outcome—	Judged on information summarized in the evidence profile and based on the criteria
5. Relative importance of outcomes—	Only important outcomes should be included in evidence profiles. The included outcomes should be classified as critical or important (but not critical) to a decision
6. Overall quality of evidence—	The overall quality of evidence should be judged across outcomes based on the lowest quality of evidence for any of the critical outcomes.
7. Balance of benefits and harms—	The balance of benefits and harms should be classified as net benefits, trade-offs, uncertain trade-offs, or no net benefits based on the important health benefits and harms
8. Balance of net benefits and costs—	Are incremental health benefits worth the costs? Because resources are always limited, it is important to consider costs (resource utilization) when making a recommendation
9. Strength of recommendation—	Recommendations should be formulated to reflect their strength—that is, the extent to which one can be confident that adherence will do more good than harm
Subsequent steps	
10. Implementation and evaluation—	For example, using effective implementation strategies that address barriers to change, evaluation of implementation, and keeping up to date

Annex 3.1: Drug information request form

ABC Facility- Drug Information Service

DRUG INFORMATION QUERY FORM								
					Date:			
					Time:		**am/pm**	am
I-Requester's contact information: *(To be filled by requester or DI pharmacist)*								
Full Name:	**Dr. Mr. Mrs. Sr.):**		Mr					
Physical address:	**Tel No:**			**E-mail:**			**Fax:**	
Qualification/Profession:	GP		Specialist		Health Officer		Patient	
	Nurse		Pharmacist		Druggist		Student	
	Other *(Please specify)*							
Method of Contact:	Walk-in		Phone		Written form		E-mail	
	Fax		Letter		Other (Please specify)			
II-Background information on query:								
The request is:	**Patient specific**			**Academic**		**Other**		
If Patient specific, *Please record patient information that you feel may be helpful in answering your request (such as patient's age, sex, weight, disease states, laboratory values, medications allergies etc…).*	**Age**		**Sex**		**wt (kgs)**	**Diagnosis**		
	Current Medication:							
	Concurrent medication/s:							
	Allergies:							
	Other information related to Patient:							
Request/Question:								
Preferred method of Response:	**Verbal**		**Phone**		**printout**	**E-mail**		
	written form				**Fax**			
Response needed in:	**prompt**		**30-60 min**		**end of day**	**when time permits**		
References required:	YES			NO				
Additional Information required:								
Initials of the requester(optional)					**Date:**		**Time:**	
For DI pharmacist use only								
Enquiry Received on (Date):					**Time:**			
Enquiry Received by:					**Enquiry Reference No.**		**DI001**	
Response given to requester on (*Date):*							**Time:**	
Response made by:								

Annex 3.2: Drug information response form

ABC Facility- Drug Information Service

DRUG INFORMATION RESPONSE FORM									
					Enquiry Reference No.:				
					Date:			**Time**	
To*(name of inquirer):*			Phone No:			Email:			
Dear									
We acknowledge the receipt of your enquiry on drug information dated								***and documented***	
under ref. No			***We are pleased to put forward the required information as follows:***						
Question/query:									
Answer/response:									
References:									
Additional information/materials and recommendations provided:									
Disclaimer:									
The DIS is designed to assist health care providers and other users to provide accurate, up-to-date, reliable and complete									
We hope we have served you with this information and in case you need further information/materials, please fill free to									
Response completed By:				Date:			Initials:		

Annex 3.3: Drug information service feedback form

DRUG INFORMATION SERVICE FEEDBACK FORM									
						Enquiry Reference No.:			
						Date of enquiry:			
Dear enquirer:									
We want to hear fr									
The _____hospital/H center DIS is seeking your feedback on the information we have provided in response									
your enquiry under				Dated				. We value your	
feedback because this helps us to stay in touch with your needs and for the continuous quality improvements of									
We invite you to use this form to submit feedback or complaint. Provision of the information requested									
1. Was the information received in time?					Yes		No		
2. Was the presentation of the information					Yes		No		
3. Did the information provided meet your					Yes		No		
4. Was the information used?					Yes		No		
5. If your answer to Question No. 4 is Yes, what was the outcome?									
6. If your Answer to Question No. 4 is No, please describe the reason why the									
7. Additional comments and suggestions on the DIS									
Name of enquirer:			Phone No:				Email:		
We thank you for your time and response									

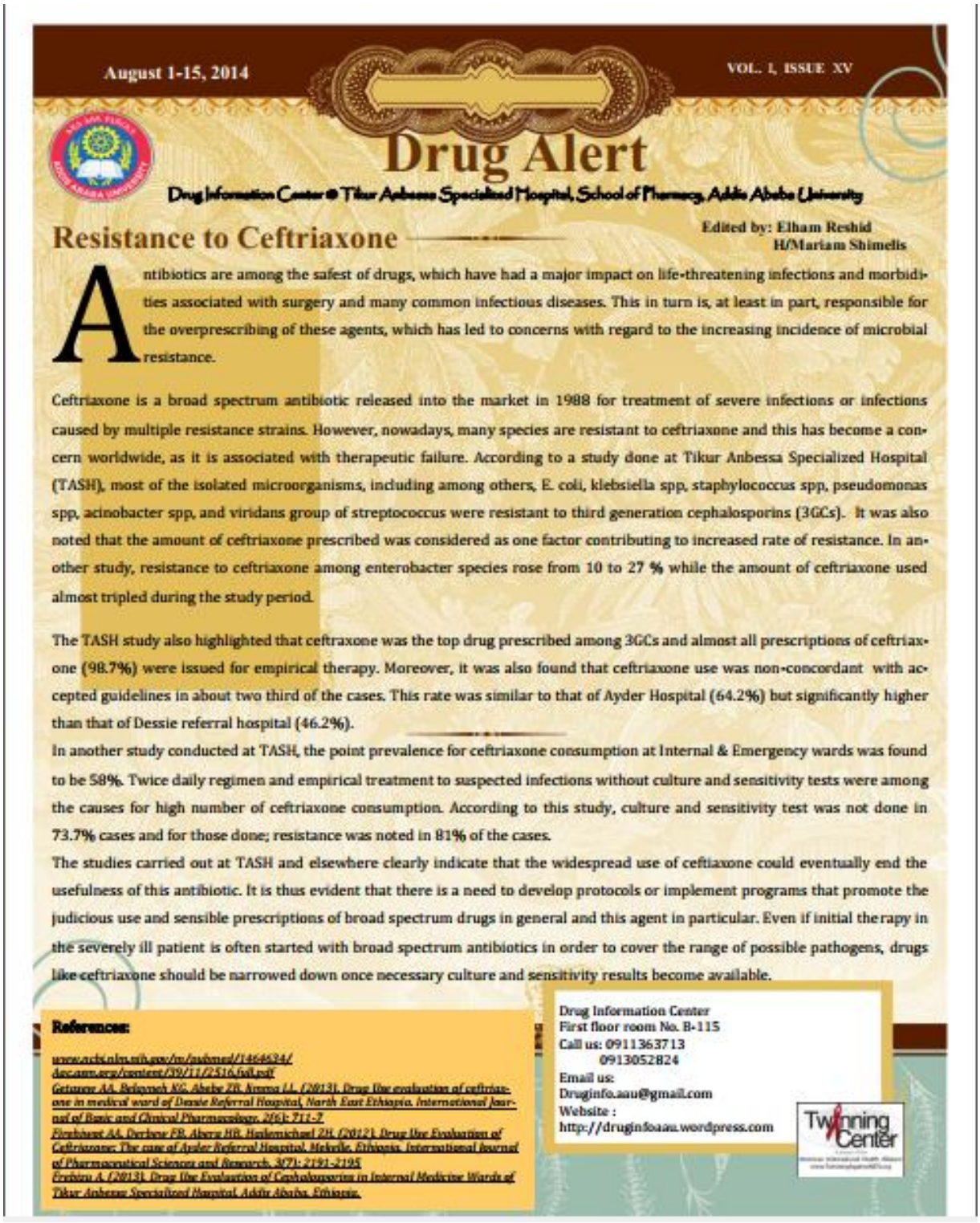
Annex 4.1. Rules to make writing more professional!

S.N.	Rule
Rule 1	Do sufficient ***research*** before getting started • There should be a deep research on articles or written credible evidences to prepare the item needed, ahead of time
Rule 2	***Organize*** the information before starting to write • Put an outline and layout
Rule 3	Put yourself in the ***reader'sposition***. • What does that reader want and how does he or she want it presented?
Rule 4	Use proper ***spelling*** and ***grammar*** • The document will be dismissed as probably wrong, based on grammar, and spelling alone
Rule 5	Try to make the write-up ***entertaining***; enjoyable & easy to read • Stay cautious with humor and within limits of professionalism
Rule 6	Document should look ***presentable*** • Papers that are crumpled, creased, torn, dirty, or coffee stained does not look professional and must be avoided.
Rule 7	Make it simple and direct; • Keep the documents as short as possible & avoid using big words to sound impressive. • Consider tables, figures, or graphs to make the document simpler and easier to understand in cases of bulkier data.
Rule 8	***Avoid*** using ***abbreviations*** or acronyms • State full form of words on first-time mentions, followed by abbreviations in parenthesis. • Units of measurement should be expressed in the metric system and laboratory measurements in terms of the International System of Units (SI).
Rule 9	Use an ***appropriate*** '***voice'*** • Avoid writing in the first person (e.g. I, we, us) and second person. • It is preferable to avoid using the passive voice throughout, use active sentences • Avoid both contractions (e.g. dep't) and slash construction (e.g. he/she)
Rule 10	Be sure to ***givecredit****through referencing* • Make sure information obtained is from the original article and expressed properly.
Rule 11	Work the document in the easiest ***order possible*** • Sort articles into groups and start with shortest & easiest information
Rule 12	***Edit*** the document thoroughly. Edit, Edit, Edit! • Go back, revise, and reorganize the document, if necessary

Annex 4.2: Sample newsletter or website topics

Newsletter or website topics
• Adherence • Advances in therapeutics • Adverse drug reactions • Calendar of events • Clinical guidelines • Clinical pearls • Compliance • Drug shortages • Drugs withdrawn from market • Effects of external events on jobs • FDA warnings • Job-related information • New information sources • New legal or regulatory requirements • New services • News from other departments • Organization's stand on issues • Patient safety • Personnel policies • Pharmacoeconomic • Pharmacogenomics • Pharmacy and therapeutics committee actions and news • Productivity improvement • Professional announcements • Review of drugs/drug classes • Quality assurance • Quality improvement

Annex 4.3: Sample drug alert (Courtesy of AAU- TASH Drug Information Services)



August 1-15, 2014 VOL. I, ISSUE XV

Drug Alert

Drug Information Center @ Tikur Anbessa Specialized Hospital, School of Pharmacy, Addis Ababa University

Resistance to Ceftriaxone

Edited by: Elham Reshid
H/Mariam Shimelis

Antibiotics are among the safest of drugs, which have had a major impact on life-threatening infections and morbidities associated with surgery and many common infectious diseases. This in turn is, at least in part, responsible for the overprescribing of these agents, which has led to concerns with regard to the increasing incidence of microbial resistance.

Ceftriaxone is a broad spectrum antibiotic released into the market in 1988 for treatment of severe infections or infections caused by multiple resistance strains. However, nowadays, many species are resistant to ceftriaxone and this has become a concern worldwide, as it is associated with therapeutic failure. According to a study done at Tikur Anbessa Specialized Hospital (TASH), most of the isolated microorganisms, including among others, E. coli, klebsiella spp, staphylococcus spp, pseudomonas spp, acinobacter spp, and viridans group of streptococcus were resistant to third generation cephalosporins (3GCs). It was also noted that the amount of ceftriaxone prescribed was considered as one factor contributing to increased rate of resistance. In another study, resistance to ceftriaxone among enterobacter species rose from 10 to 27 % while the amount of ceftriaxone used almost tripled during the study period.

The TASH study also highlighted that ceftraxone was the top drug prescribed among 3GCs and almost all prescriptions of ceftriaxone (98.7%) were issued for empirical therapy. Moreover, it was also found that ceftriaxone use was non-concordant with accepted guidelines in about two third of the cases. This rate was similar to that of Ayder Hospital (64.2%) but significantly higher than that of Dessie referral hospital (46.2%).

In another study conducted at TASH, the point prevalence for ceftriaxone consumption at Internal & Emergency wards was found to be 58%. Twice daily regimen and empirical treatment to suspected infections without culture and sensitivity tests were among the causes for high number of ceftriaxone consumption. According to this study, culture and sensitivity test was not done in 73.7% cases and for those done; resistance was noted in 81% of the cases.

The studies carried out at TASH and elsewhere clearly indicate that the widespread use of ceftiaxone could eventually end the usefulness of this antibiotic. It is thus evident that there is a need to develop protocols or implement programs that promote the judicious use and sensible prescriptions of broad spectrum drugs in general and this agent in particular. Even if initial therapy in the severely ill patient is often started with broad spectrum antibiotics in order to cover the range of possible pathogens, drugs like ceftriaxone should be narrowed down once necessary culture and sensitivity results become available.

References:

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Firehiwot A. (2013). Drug Use Evaluation of Cephalosporins in Internal Medicine Wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

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First floor room No. B-115
Call us: 0911363713
0913052824
Email us:
Druginfo.aau@gmail.com
Website :
http://druginfoaau.wordpress.com

Twinning Center

Annex 4.4: Sample newsletter (Courtesy of SPHMMC Drug Information Services)

SPHMMC- Drug Information Service

Safety of Using Expired Medications

VOL 1, Issue 1: July

Inside this issue:

Prepared: Abraham Sisay
(Clinical Pharmacist)
Edited: Kalkidan G/medik
(Clinical Pharmacy Specialist)

Expiration date is the final day that the manufacturer guarantees the full potency and safety of a medication. Once the original container is opened, the original expiration date cannot be longer relied up on.

Stability studies have shown the actual shelf life of the drug may be much longer that expiration date. However it is difficult to know which product could have an extended shelf life. The ability to have an extended shelf life would be dependent upon the actual drug ingredients, Presence of preservatives, temperature fluctuation, humidity and other storage conditions.

Solid dosage forms appear to be most stable while solution or reconstituted suspension may not have required potency if used when outdated and should be discarded if the product forms a precipitant or looks cloudy or discolored.

Medications used in life-threatening situations,

Even though there is no evidence that using expired medications for non-life threatening conditions is unsafe, given the storage and transportation conditions in our locale, it is not recommended.

http://www.drugs.com/article/drug-expiration-dates, accessed on 30th Dec. 2014.

Facts you need to know about Ceftriaxone

Ceftriaxone is a third generation cephalosporin which does not require dose modification in the presence of severe renal failure.

Ceftriaxone with dextrose injection is intended for IV administration ONLY, While Ceftriaxone sodium injection may be administered IV or IM.

Reconstituted solution of ceftriaxone should be light yellow to amber; not to be administered if solution is cloudy or any precipitate is present.

Ceftriaxone, if given by IV, should be infused over 15- 30 minutes in adults and over 10-30 minutes in neonates or children.

When giving IM, inject deeply into large muscle like upper outer quadrant of gluteus muscle, or lateral thigh. Use aspiration to ensure that the needle is not in a blood vessel.

IM solutions prepared using bacteriostatic water containing benzyl alcohol should not be used in neonates.

Because of the possibility of precipitation of ceftriaxone calcium: IV ceftriaxone should NOT be administered with Calcium containing IV solution

And reconstituted vials should NOT be further diluted for IV administration.

For patients other than neonates, ceftriaxone and calcium-containing solution may be administered sequentially if infusion lines are thoroughly flushed with a compatible fluid like DW, NS, bacteriostatic water, or water for in-

Disclaimer:- This is a supplemental medication related information, not intended to be a replacement for appropriate pharmaceutical care.

Annex 4.5: Format for drug evaluation monograph

***Generic Name**:* Can include other common, nonofficial names, e.g., TPA for alteplase.

***Trade or Brand Name**:* If more than one, indicate company that each is from.

***Manufacturer (or source of supply)**:* Include website address.

***Therapeutic Category**:* For example, thrombolytic agent for alteplase.

***Classification**:*

Status: Prescription, nonprescription, and/or controlled substance schedule (if applicable).

***Similar Agents**:* A list of common treatments used for the same indication(s).

Pharmacologic Data

- Mechanism of action (usually brief)
- Bacterial spectrum (if applicable)
- ***Bioavailability/Pharmacokinetics**:*
    - A table summarizing the following, in comparison to the comparator agent(s) can be very useful.
    - Absorption
    - Distribution
    - Metabolism
    - Excretion

Therapeutic Indications

- Food and Drug Administration (FDA)-approved indications-clearly indicate which indications are FDA approved.

- Potential unlabeled uses (list only if they are considered to be acceptable medical practice, although it is allowable to mention others that are early in investigation with a statement that the drug should not be used for them or that they require more study)—clearly indicate they are not FDA approved.

Dosage Forms

- Forms and strengths: Compare to other agents (consider a table), since new products often have a limited number of dosage forms/routes as compared to established products. Purity and composition information should be included for herbal and alternative medications.

- Explain any special information needed for preparation and storage, in comparison to other products. Sometimes a product will be so difficult to prepare or have such a limited shelf-life after preparation that it is not worth stocking.

Dosage Range

- Adults

- Children
- Elderly
- Renal or hepatic failure

Special administration requirements

- Any anticipated problems in supplies (i.e., shortages) or restrictions in distribution (e.g., physician needs to be certified to prescribe)

Known Adverse Effects/Toxicities

- Frequency and type (a table comparing the drug to others can be a clear and concise way of expressing this information)

- Prevention of toxicity

- Risk and benefit data

Special Precautions*:* Usually includes pregnancy and lactation

Contraindications

Drug Interactions*:* A simple one- or two-sentence statement for each—usually separate various interactions into separate short paragraphs and compare to other drugs.

- Drug-drug
- Drug-food
- Drug-laboratory

Patient Safety Information

Includes medication error information

- ***Patient Monitoring Guidelines***

Includes effectiveness, adverse effects, compliance, and other appropriate items

- ***Patient Information***
    - Name and description of the medication
    - Dosage form
    - Route of administration
    - Duration of therapy
    - Special directions and precautions
    - Side effects
    - Techniques for self-monitoring
    - Proper storage
    - Refill information
    - What to do if a dose is missed

Cost Comparison*:* Use Average Wholesale Price (AWP) and institutional prices, and make sure there is a comparison with any similar products at equivalent doses—a pharmacoeconomic analysis is the best method of comparing drugs in this section; remember to include any required concomitant therapy. Providing a spreadsheet file with information to consider different circumstances may be helpful.

Summary:Includes a short summary of advantages and disadvantages of the drug, particularly in relation to other drugs or treatments used for each major indication, and any other significant information.

Recommendations*:* Indicate whether the drug should be added to the Drug Formulary of an institution, assuming they would have patients that would be treated for illnesses where this drug might be used. Also indicate specific formulary status for the drug (i.e., uncontrolled, monitored, restricted, and conditional) and whether the drug will replace any other product that might already be on the formulary. In addition, present any information on how the drug is to be placed in any clinical guidelines.

Annex 4.6: Sample Monograph:(Detail)

VARDENAFIL (LEVITRA®)

I. THERAPEUTIC CLASSIFICTION: Type 5 phosphodiesterase (PDE-5) inhibitor.

II. DRUGS: Sildenafil (Viagra®), Tadalafil (Cialis®), and Vardenafil (Levitra®)

III. DESCRIPTION: Vardenalfil (Levitra®) is an oral therapy for the treatment of erectile dysfunction. This monohydrochloride salt of vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5)[1-3] In addition to facilitating tumescence, drugs in this class shorten the refractory period associated with subsequent ejaculation. They are also effective in both iatrogenic and disease-related ED, including that resulting from diabetes or prostatectomy.[3]

IV. INDICATIONS (FDA and Non-FDA approved Indications):

Drug Comparisons The drug can be used for the following conditions.	Sildenafil	Tadalafil	Vardenafil
altitude sickness	yes	No	no
anorgasmy	yes	No	no
erectile dysfunction (ED)	yes	yes	yes
pulmonary hypertension	yes	No	no

V. PRICE COMPARISON (July 2005) [4]

DRUG STRENGTH	PRICE
Levitra 2.5, 5, 10, 20 mg	$3.54/tab*
Viagra 25 mg	$5.82/tab
Viagra 50, 100 mg	$5.72/tab
Cialis 5 mg	$6.13/tab
Cialis 10 mg	$6.07/tab
Cialis 20 mg	$6.18/tab

VI. DOSE AND ADMINSTRATION:

Table 2. Dosage Parameters for Sildenafil, Vardenafil, and Tadalafil			
Parameter	**Sildenafil**	**Vardenafil**	**Tadalafil**
Initial Dose	50 mg	10 mg	10 mg
Dosing Range	25-100 mg	2.5-20 mg	5-20 mg
Maximum Dose	100 mg	20 mg	20 mg
Dose Adjustments	• Age > 65 years, hepatic impairment: 25 mg • Severe renal impairment (CrCl < 30 ml/min): 25 mg	• Age > 65 ys: 5 mg • Moderate hepatic impairment: initial 5 mg, max 10 mg • No adjustment needed in renal impairment:	• Age > 65 y: no dosage adjustment • Mild or moderate hepatic impairment: max 10 mg once daily • Severe hepatic impairment: not recommended • Moderate renal impairment: initial 5 mg once daily, max 10 mg every 48 hours • Severe renal impairment (CrCl < 30 ml/min) on hemodialysis: max 5

			mg
Onset	Take 60 minutes prior to sexual activity	Take 60 minutes prior to sexual activity	Take prior to anticipated sexual activity

VII. PHARMACOLOGY: Nitric oxide is released in the corpus cavernosum of the penis during sexual stimulation, which subsequently activates guanylate cyclase. This enzymatic activation results in increased concentrations of cyclic guanosine monophosphate (cGMP), the trigger for smooth muscle relaxation, which facilitates increased blood flow and thereby produces an erection (tumescence). Sildenafil, tadalafil, and vardenafil potentiate work by inhibiting PDE5, the substance responsible for degrading cGMP in the corpus cavernosum.[3,4]. However, sexual stimulation is required for the medications to be effective, leading some to characterize PDE5 inhibitors as facilitators rather than instigators of tumescence. [1]

The authors of 4 independent studies that compared the three agents that are currently on the market have noted an overall efficacy for PDE-5 inhibitors of 81% to 91% in clinical practice.[5,6] It is reassuring that even with varying methodologies efficacies are quite consistent across studies and drugs. The studies by Stroberg[6] and Claes[7] are quite noteworthy in that they found no statistically significant patient preferences in treatment-naive patients and an 8% to 10% no-response rate with PDE-5 inhibitors. The unanimous use of the IIEF and especially the Erectile Function Domain scores suggests a universal acceptance of these tools in both premarketing and post marketing drug studies, something that cannot be said for questionnaires dealing with preference. When preference is based on "time concerns," tadalafil will be selected by most patients. None of these investigations was blinded. It is essential in going forward with comparison trials that we strive for unbiased methodology. The Figure suggests a possible method of masking treatment in these studies of drugs with highly recognizable forms.

VIII. DRUG INTERACTIONS: Increased QTc intervals have been reported, the longest with vardenafil, shortest with tadalafil, and intermediate with sildenafil. There may be interactions with other medications metabolized in a similar way, such as erythromycin and HIV protease inhibitors.[9]

Drug Comparisons The drug interacts with the following drugs:	**Sildenafil**	**Tadalafil**	**Vardenafil**
Amiodarone	no	yes	yes
all Beta-agonists	no	No	yes
Chloroquine	No	No	yes
Ciprofloxacin	No	No	yes
all Class IA antiarrhythmics	No	No	yes
all Class III antiarrhythmics	No	No	yes

Clozapine	No	No	yes
Cyclobenzaprine	No	no	yes
Dexamethasone	no	yes	yes
Dolasetron	no	no	yes
Droperidol	no	no	yes
Isoniazid INH	no	yes	yes
all Local Anesthetics	no	no	yes
Nitroprusside	yes	no	no
Propafenone	no	no	yes
Risperidone	no	no	yes

all Tricyclic antidepressants	no	no	yes

Ziprasidone	no	no	yes

IX. ADVERSE EFFECTS: The most common adverse effects of PDE 5 inhibitors therapy are headache (16%), flushing (10%), and dyspepsia (7%). Other side effects are as follows:

Abnormal vision: in response to postmarketing reports of the vision loss in men taking type PDE-5 inhibitors, the US Food and Drug Administration (FDA) has issued a news release to advise healthcare providers of the potential risk. FDA has received 43 reports of varying degrees of vision loss, including blindness, among users of these drugs -- 38 cases in men using sildenafil, 4 in men using tadalafil, and 1 case in a man using vardenafil. including light sensitivity and color impairment (e.g., blue tints of vision). The overall incidence may be up to 3% of patients, particularly those receiving doses in excess of 100 mg.[8] Such experiences are more characteristic of sildenafil's weak inhibitory effect on PDE6. Most of these cases of vision loss were due to nonarteritic anterior ischemic optic neuropathy (NAION). The loss of vision in some cases has been irreversible.

Priapism and prolonged erection are rare adverse events. Priapism, occurs sometimes to the extent of at least 6 hours, have also been reported with the agent. These adverse effects are similarly noted with the two newer agents.

Spontaneous death:Despite sildenafil's relatively benign adverse effect profile, a number of cases of morbidity and mortality related to cardiovascular events have been reported since the drug's introduction. A 1999 summary of postmarketing surveillance revealed that 77 of 130 verified deaths possibly associated with sildenafil were cardiovascular in nature. These deaths included 41 cases of definite or suspected myocardial infarction (MI).[9]In an evaluation of these reports of deaths associated with sildenafil, the FDA concluded that there was no deducible evidence of an increase in the mortality rate among sildenafil users compared to the general population. According to the initial studies conducted, vardenafil and tadalafil demonstrate efficacy data approximately comparable to those of sildenafil.

Myalgia: The overall safety of the treatments is good, even in patients with a history of cardiovascular disease. This agent does, however, have increased affinity for PDE11, commonly found in skeletal muscle and other organs. Patient complaints of myalgia and back pain may be related to this mechanism.[1,5] Reports of significant safety concerns with tadalafil and vardenafil have yet to be published.

Hypotension: Inhibition of PDE5, a substance present throughout the vasculature, produces hypotension.[8] Systolic and diastolic pressures may be diminished by 8-10 mm Hg and 5-6 mm Hg, respectively, following these agent administration. The drug potentates the decrease in blood pressure resulting from nitrates, and concurrent use with such agents is contraindicated. Caution should be exercised with concomitant administration of alpha-adrenergic receptor blockers.

Arrhythmia: One potentially significant difference among the drugs, however, is vardenafil's potential for prolongation of the QTc interval, a phenomenon associated with ventricular dysrhythmias and sudden cardiac death.[8] Although no reports of this problem have been published, patients should be carefully screened and monitored. Vardenafil should not be administered to patients with congenital QTc prolongation or those receiving Class IA or III antiarrhythmic agents. Cardiac conduction disorders are also more likely when the PDE5 inhibitor is used concomitantly with CYP 3A4 inhibitors (e.g., itraconazole, ketoconazole, erythromycin).

X. WARNING/PRECAUTION:

Drug Comparisons The drug is contraindicated in or should be used cautiously in the following conditions:	**Sildenafil**	**Tadalafil**	**Vardenafil**
Angina	yes	yes	yes
aortic stenosis	yes	no	yes
cardiac	yes	yes	yes

arrhythmias			
coagulopathy	yes	no	yes
females	No	yes	no
gastroesophageal reflux disease (GERD)	yes	yes	yes
heart failure	yes	yes	yes
hepatic disease	yes	yes	yes
hypertension	yes	yes	yes

hypotension	yes	yes	yes
hypovolemia	no	yes	no
idiopathic hypertrophic subaortic stenosis	yes	No	yes
myocardial infarction	yes	yes	yes
nitrate/nitrite therapy	yes	yes	yes
QT prolongation	No	no	yes

renal disease	No	no	yes
renal failure	No	no	yes
renal impairment	yes	yes	yes
retinitis pigmentosa	yes	yes	yes
stroke	yes	yes	yes
visual disturbance	yes	yes	yes

XI. PHARMACOKINETICS: All three agents have some effects on other phosphodiesterase isoenzymes, including types 1-4 and 6. Tadalafil has a lesser affinity for PDE6 but greater effects on PDE11.[1] Sildenafil is rapidly absorbed following oral administration, with an absolute bioavailability of 40%. Peak concentrations are achieved approximately 1 hour following extensive first-pass metabolism.[1] Time to onset of clinical effects ranges from 14 to 60 minutes.[5] A more rapid onset of effects has been noted with the two newer agents. Sildenafil and vardenafil show some interaction with food intake. Time to onset of action is usually 30-120 minutes, but there are reports of shorter times to onset of action. The duration of action of sildenafil and vardenafil is about 4 hours, whereas that of tadalafil is about 36 hours. The primary route of sildenafil metabolism is the cytochrome (CYP) P450 system through the 3A4 pathway, with some metabolism occurring via the 2C9 isoenzyme. Protein binding reaches 96%, and the elimination half-life of both the parent compound and active metabolite *N* -desmethyl sildenafil is 3 to 5 hours.[1] The metabolites are excreted via the fecal route.

XIII. RECOMMENDATIONS:Don't add to the formulary

Positive:

- Efficacy
  - All the three drugs are effective treatments for ED by inhibiting PDE-5 (efficacy: 81-91%)
  - Also effective in iatrogenic, diabetic mellitus, and prostatecotomy-induced ED.
- No dose adjustment needed in renal or hepatic impairment
- Cost
  - 40% less expensive than Viagra
  - 50% less expensive than Cialis
- Pharmacokinetics
  - More rapid onset than sidenafil and less time to onset comparing to tadalfil
  - It has a shorter onset of action comparing to tadalfil
- Toxicity
  - Less visual impairment toxicity report: Tadalafil and vardenafil are safer in this regard because of their greater selectivity for PDE-5 than sildenafil.
  - Sildenafil has the most visual toxicity.
  - Not associated with sudden death (there are reports for Viagra)
- No report of myalgia unlike sildenafil

Negative

- Indications:
  - Vardenafil has the least number of indications; Viagra has the highest
- Toxicity: Causes the highest incidence of QT prolongation
  - High potential to cause arrhythmia
  - Drug interactions:All of them interact with nitrates and alpha blockers.
  - However, Levitra has the highest number of drug interactions
  - Because of its QT prolongation effect (interacts with all antiarrhytmics and CYP455 3A4 drugs)
- Patient compliance
  - Less preferred by patients based on "Time concerns".
- Pharmacokinetics
  - because tadalafil has a longest half-life and dosed q36 hours vs. q4 hours
  - This may allow greater spontaneity and less frequent dosing of tadalafil but may also prolong adverse effects.

Annex 4.7.Sample Monograph: (Short form-for information dissemination)

Janumet (50 mg Sitagliptin and 500, 850, 1000 mg film coated tablets)

***Indication*:** Janumet is indicated as a triple therapy in combination with a Sulphonylurea/thiazolidinedione as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a suphonylurea/thiazolidinedione/insulin.

Dose: As recommended by doctors but it should not exceed the daily dose of 100 mg sitagliptin.

Side effects: The main side effects related to sitagliptin are headache, hypoglycemia, constipation, and dizziness. Metformin was mainly associated with gastrointestinal symptoms.

Interaction: Interactions are related to individual drugs but not the combination. There is an increased risk of lactic acidosis in alcohol intoxication. Cationic medicinal products like cimetidine may interact with metformin by competing for common renal tubular transport system. The intravascular administration of iodinated contrast agents may result in renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

Contraindications: Those patients allergic with the active ingredient or any of the list products in the drug. It is contraindicated in individuals with diabetic ketoacidosis, moderate and severe renal impairment (creatinine clearance <60ml/min), acute condition with a potential to alter renal functions (Dehydration, severe infection, shock, and intravascular administration of iodinated contrast agents), hepatic impairment, and alcohol intoxication. It is also contraindicated in women who are breastfeeding.

Precautions: The excretion of the drug is by kidney and thus dependent on renal function. Lactic acidosis should be checked in patients with renal problems and elderly patients. Dose of other anti diabetic medications should be decreased while they are given with Janumet to decrease risk of hypoglycemia. Cautions also should be taken when Janumet is given with the above interacting drugs. Diuretics and beta 2 agonists have intrinsic hyperglycemic effects while angiotensin Converting Enzyme inhibitors decrease blood glucose level. Thus, the dose of Janumet should be adjusted accordingly.

Annex 5.1: Sample facilitator note on basic facts about insulin

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›="c<K=" U"É" '¨<;

›="c<K=" qi*ƒ* ŸT>vM ¾›"L‹" ¡õM ¾T>S'ß "Ø[pSU (Hormone) c=J" ¾T>c^¨<U Ÿý*a*+" '¨<::

›="c<K=" Kc¨<'•‹" KU"ÁÅeðMÒM;

u›"L‹" ¨<eØ Ÿ}KÁ¿ ¾UÓw ¯Ã'„‹ ¾T>Ñ–¨<" e"D` u›Óvu< ¨ÅT>ðKÑ¨< ØpU LÃ KTªM ›="c<K=" ¾}vK¨< "Ø[ pSU }}Ÿ= ¾K?K¨< }Óv` ÃðîTM:: eK²=I ¾›="c<K=" e^ Ÿ}e}ÕÔK uÅT‹" ¨<eØ ¾e"D` SÖ" ÃÚU^M:: ›="c<K=" u}ÚT]U K?KA‹ }Óva‹ ›K<*ƒ*::

¾›="c<K=" I¡U" ¾T>ÁeðMÑ¨< K¾*ƒ*—¨< ¾e"D` ISU ¯Ã'*ƒ* '¨<;

¾›="c<K=" I¡U" K¾*ƒ*—¨<U ¾e"D` ISU ¯Ã'*ƒ* K=ÁeðMÓ Ã‹LM:: 'Ñ` Ó" K›"Å—¨< ¯Ã'*ƒ* ¾e"D` ISU (Type 1 Diabetes) ISS< Ÿ•¨ku*ƒ*Ñ>²? ËUa dÃ²ÑÃ¾›="c<K=" I¡U" SËS` ›Ku*ƒ*::¾²=I ¯Ã'~ u›w³—¨< uIí"*ƒ*" u¨×„‹ LÃ¾T>Ÿc*ƒ* c=J"¾e"D` ISU õì<T©¾›="c<K="ºØ[*ƒ* (absolute insulin deficiency) eLK Ÿ›="c<K=" ue}k` K?L U"U ›T^ß I¡U" •"ÅK?K¨< K=•¨p ÃÑvM::•"Ç=G<U KSËS]ÁÑ>²? U•`Ó'"¨p*ƒ* KT>Ÿc*ƒ*¾e"D` ISU (Gestational Diabetes) •" T"—ªU ¾e"D` ISU ÁL*ƒ* •"*ƒ* K•`Ó'" KS²ÒË*ƒ*U J' u•`Ó'" ¨p*ƒ* ¾e"D` SÉ•'*ƒ* ›eðLÑ> J•Ÿ}Ñ–Ÿ›="c<K="¨<Ü K?KA‹"¾e"D` SÉ'>„‹ (oral hypoglycemics)SÖkU ›ÃSŸ`U::

u›G<'< Ñ>²? u›Ñ^‹" U" ¯Ã'*ƒ* ›="c<K=" uØpU LÃ ÃÑ—M;

u›G<'< ¨p*ƒ* u›=*ƒ*ÄåÁ ¨<eØ uØpU LÃ ÁK<*ƒ* ¾›="c<K=" ›Ã'„‹ G<K*ƒ* "†¨<::•'c<U:-

1. uõØ'*ƒ* Se^*ƒ* ¾T>ËU`" ›ß` c¯•*ƒ*"¾T>c^ ¾›="c<K="›Ã'*ƒ* (Short acting insulin) ¨ÃU _Ñ<L` (Regular) ›="c<K=" }wKA ¾T>Ö^¨< ¨<G SM¡ ÁK¨< ðdi '"

2. [²U LK c¯*ƒ* ¾T>c^" uk" Ÿ1 eŸ 2 Ñ>²? ¾T>cØ ¾›="c<K=" ›Ã'*ƒ*' Éõ`e (Ñ<U) SM¡ ÁK¬ ðdi "†¨<:: '²=I ¾›="c<K=" ›Ã'„‹" u›"É LÃ uTªHÉ ¾T>²Ò¦ ¾›="c<K=" ›Ã'„‹U ÃÑ—K<:: SM"†¨<U Éõ`c<" ¾›="c<K=" ›Ã'*ƒ* ÃSeLM:: K•Á"Ç"Æ ¾e"D` ISU}— NŸ=S< uT>S¡[¨< Sc[*ƒ* ›"Æ" ¨ÃU G<K~" ¾›="c<K="¯Ã'„‹ ¨ÃU kÉS¨< }ªIÅ¨< ¾}²Ò¦ ¾›="c<K=" ¯Ã'„‹" SÖkU ÃSŸ^M:: ŸLÃ ¾}²[²\*ƒ* ¾›="c<K=" ¯Ã'„‹ u}KÁ¾ ¾"ÓÉ eU uÑuÁ LÃ eKT>Ñ– ISU}—¨< ¾}K¾¾›="c<K=" ¯Ã'*ƒ* ŸS¨<cÆ uò*ƒ* }Ñu=" KISS< ¾•²²K*ƒ*"›="c<K=" K=}" ¾T>‹M SJ'<" ŸÖ?" vKS<Á U¡` K=ÁÑ˜ ÃÑvM::

Ÿ›="c<K=" I¡U" Ò` u}ÁÁ² U" Ø"no TÉ[Ó eðMÒM;

1) ›="c<K=" uk´n³ x•Ÿ}Ñ–U uTk´k¹¨<eØ¾p´n²?¨< SÖ"Ÿ4 - 8^{O}C ¾T>J"u*ƒ* ¾Tk´k¹ ¡õM ¨<eØ TekSØ:: uu?*ƒ* ¨<eØ SÑMÑÁ Tk´k¹ ÃI ¾p´n²? SÖ" ¾T>Ñ–¨< u›*ƒ*¡M*ƒ* TekSÝ¨< ¾•‹—¨<¡õM ¨<eØ'¨<:: ›="c<K="" uTk´k¹¨< u` LÃ TekSØ u}ÅÒÒT>Ñ>²? ¾u\ SŸð*ƒ*" S²Ò*ƒ*¾›="c<K='<" S<k*ƒ*" p´n²? SÖ" Sª¶p eKT>ÁeŸ*ƒ*M x• LÃ vÃkSØÃSŸ^M:: Tk´k¹ uK?Ku*ƒ*›"vu= ›="c<K=" k´k´ vK' kØ• ¾ìHÃ w`H" uTÃÅ`eu*ƒ* um ¾›¾` '¨<¨<` vKu*ƒ* ¾u?~ ¡õM SkSØ Ã‹LM:: u×U Vn*ƒ* uJ'< ›"vu=•‹Ÿg¡L ¾}c\ •"ÅÉe*ƒ*ÁK<ºn•‹¨ÃU ›gª¨<eØ TekSØ p´n²?¨<"Öwq •"Ç=qÃ Ã[ÇM:: ›"É SÖkU ¾ËS`'¨< ¾›="c<K=" wMnØ ¾u?*ƒ* ¨<eØ S<k~ Ÿ25^{O}C uTÃuMØ •"Å ›Ç=e ›uv ¯Ã'*ƒ* ›"vu•‹Ÿ1 ¨` LMuKÖÑ>²? ŸTk´k¹¨<Ü ŸìHÃ w`H" Öwq TekSØ" SÖkU Ã‰LM::

2)¾›="c<K=" S¨Ñ>Á x••‹" u¾•K~ uØ"no SS`S`:: u}ÅÒÒT>›"É x• LÃ ›="c<K=" S¬Ò*ƒ* ¾S¨Ñ>Á x••‹" TuØ¨ÃU SÕÔM ÁeŸ*ƒ*LM:: ÃI ux•¨< LÃ¾}¨Ò¨<›="c<K=" uum SÖ"¨ÅÅU •"ÇÃÑv" um e^ •"ÇÃc^ ÁÅ`ÑªM:: eK²=I ¾S¨Ñ>Á x•‹"ŸS¨Ò'" uò*ƒ*›ekÉS" uØV" SSMŸ*ƒ* SÇce ÁeðMÒM:: ¾ÕÔK" ÁuÖ x• LÃU ›="c<K=" S¨Ò*ƒ*›ÃÑvU' ÃI""U ‹Ó` KTe¨ÑÉ u¾•K~ ¾S¨Ñ>Á x• SKª¨ØÃÑvM::

3) ¾›=”c<K=” wMnØ” e”Ñ³U J’ SÖkU e”ËU` ¾›ÑMÓKAf ²S’< ÁLKð SJ’<” ¾}íðuf” k” SSMŸf“ k’< ÁKð ›=”c<K=” ›KSÖkU ÁeðMÒM::

4) ›=”c<K=”” KS¨Òf e“²ÒÏ KTªHÉ wMnÖ<” ŸS¨’¨’ ÃMp uG<K~ Đ‰‹” SHM K}¨c’< Ñ>²?Áf T”ŸvKM ÃS[xM:: GÃM ÁK¨< S¨’¨’ ›=”c<K=’<” K=ÔÇ¨< Ã‹LM::

5) ¨<GT¨<” (_Ñ<L`) ›=”c<K=” ŸÉõ`c< (NPH) ›=”c<K=” Ò` kLpK” ”É”¨Ò Ÿ•²²M” KSkLkM ›ekÉV ¨<GT¨<” kØKAU Éõ`c<”›=”c<K=” u›”É S`ô¨<eØ kÉ}”¨Ç=Á¨< S¨Ò$f$ÁeðMÒM:: ŸkLkM” u%EL Ÿ5 Åmn KuKÖÑ>²? TekSØ›ÃSŸ`U:: J•U ISU}— ¨<ŸS[Ö¨ÃU KSkLkM Ÿ}†Ñ[¨ÃU uNŸ=S< Ÿ}SŸ[G<K~”U u}KÁ¾ S`ô K¾w‰ S¨Òf Ã‹LM::

6) uÑ<µ LÃ ŸJ’<

- G<K?U um ›=”c<K=”“ S`ô ÃÁ²<
- IÒ© ¾GŸ=U ¾›=”c<K=” T²¹ u•Ï• u=•` ÃÖpU••M::
- ›=”c<K=”•” u•Ï¨ÃU ufŸh x`d•ÃÁ²<ŸT>Ý”°n Ò` ›ÃkLpK<::
- ›=”c<K=” ukØ• Ÿu[Ê ”Ÿ=Ÿ= •”Ç=•[¨< ›É`Ñ¨< ›ÃÁ²<' k´pµ ¾[Ò ›=”c<K=” K=uLi Ã‹LM::

7) ›=”c<K=’<” ŸSpÇf• uòf›¾` ¨Å wMnÖ<¨<eØ uc=]”lÃÚU\:: ÃIU ›=”c<K=” ¾Spf H>Å~” ÁkMM••M::

8) ¾S¨Ñ>Á x••‹”Ö”pk¨<Ã¨l' ›=”c<K=”” uJÉ' uß”¾òf Kòf¡õM' ¾uLÃ—¨<¾¡”É¡õM •“¾¨<Ü—¨<¾SkSÝ¡õM LÃ S¨<ÒfÃ‰LM:: Ÿ’²=IU eõ^•‹ uJÉ LÃ¾T>¨Ö¨<›=”c<K=” u}hK õØ’f ¨Å ÅU c=Å`e uß” LÃ ¾T>¨Ò¨< ›=”c<K=” Ó” $f$”i ²Ó¾$f$ ÃLM:: J•U Ó” Ãl u›=”c<K=” ›c^` LÃ ¾ÔL }î•› ›ÁdÉ`U:: ¾›"M wn$f$ •”penc? KTÉ[Ó e“ew ›ekÉS” ¾U”¨eÅ¨<” ›=”c<K=” Ÿõ}— •”penc? uT>ÁÅ`Ñ¨< ¾c¨<’•‹”¡õM LÃ v”¨ÒÃS[xM:: KUdK? ¾U“Å`Ñ¨<•”penc? \Ý ¨Ã ¾•Ó` Ñ<µ ŸJ’ kÉS” ¾U”¨Ò¨<” ›=”c<K=” Ÿß“‹” ÃMp uJÇ‹” LÃ w”¨Ò ÃSŸ^M:: w²<•”penc? ¾T>ÁÅ`Ó ¾›"M ¡õM ¾›=”c<K=’<” ¨Å ÅU SÉ[e ŸT>ðKÑ¨< uLÃ eKT>ÁðØ’¨< Ke"D` TKp K=ÁÒMÖ” Ã‹LM::

9) ¾›=”c<K=” ›¨ÒÓ

- S¨Ñ>Á x•” u¨<• w‰ TîÇfÃunM ÅÒÓV u›M¢M SØ[Ó ¾qÇ SÉ[p K=ÁeŸf Ã‹LM::
- ¾U”¨Ò uf” x• u×„‰‹” SHM ŸÁ’” u%EL ukØ•¨Å¨<eØ S¨<Òf
- u×U kß” ¾J’< IS<T” ¨ÃU ¾U”¨Ò uf S`ô [»U ŸJ’ S`ô¨<” u45 ዪግ፫ዘ”uM ›É`Ô S¨Òf Ã‰LM::
- ¾S¨Ñ>Á x•¨< uf”g<ÅU u=ÁdÃ‹Ó` ›ÁeŸfMU::

10) ¾›=”c<K=”” ¨Å ÅU ¾SÉ[e õØ’f” ¾T>K¨<Ö< G<’@••‹” SÑ”²w

G) ŸT>Ñv¨< uLÃ õØ’~” ¾T>ÚU\

- S<p h¨` X¨<“
- ¾S¨Ñ>Á eð^¨<” Tgf
- ¨ÅÖ<”‰ ²Mq S¨<Òf
- ¾}¨Ò¨< ›"M ¡õM LÃ eþ`•©”penc? c==•`

K) ŸT>Ñv¨< u•‹õØ’~”¾T>k”c<

- U”U •”penc? ›KTÉ[Ó
- ŸSÖ” ÁKð p´n²?
- ¾ÕÔK ¨ÃU ÁuÖ x• LÃ S¨Òf

11) ¾•²²¨<"›="c<K=" SÖ"ŸSK¨Ø uòƒ¾T>Ÿ}K<ƒ" TÖ?" ÁeðMÒM'

- ›="c<K='< u›Óvu< SÁ²<" dÃuLi SkSÖ<"
- ¾•²²¨<"¾›="c<K=" SÖ"Öwq S¨cÆ"
- ›="c<K='<" u›Óvu< TªHÉ' SpÇƒ' •" S¨Òƒ Å"x‹" SŸ}M"
- ¾S¨Ñ>Á x•¨<ÁLuÖ¨ÃU ÁMÕÔK SJ'<"
- uvKS<Á¨< ¾}SŸ[¨<" ¾›SÒÑw'¾•"penc? SS]Á•‹" u›Óvu< SŸ}M" T[ÒÑØ

12) ¾›="c<K=" SÖ"" SÚS` ›eðLÑ> ŸJ'

- u›"É Ñ>²? ›"Æ" ¾›="c<K=" ›Ã'ƒ w‰ SÚS`
- udU"ƒ Ÿ›"É ¨ÃU ŸG<Kƒ Ñ>²? ¾uKÖ ¾›="c<K=" SÖ" ›KSÚS`
- u›"È Ÿ2 - 4 ¿'>ƒ ›="c<K=" ÁMuKÖ SÚS` "†¨<::

uTÖnKÁU ›"É ›="c<K=" ¾T>¨eÉ ¾e"D` ISU}— ÁM}KSÅ ¾e"D` Sw³ƒ ¨ÃU T'e Ÿ}Ÿc}uƒ" ŸLÃ u}Ökc<ƒ S"ÑÊ‹ ðØ• "M}e}"ŸK w²< Ñ>²? dÁv¡" ¾Ö?" vKS<Á U¡` K=ÖÃp ÁeðMÒM:: u}ÚT]U ›="c<K=" ›G<" dÃ"e vKuƒ ¾ÉÑƒ Å[Í u›õ uT>ªØ SM¡ ÁM}²ÒË" uS`ô T>¨cÉ SJ'<" SÑ"²w ÃÖpTM::

Annex 5.2 (sample role play checklist)

Role Play checklist	Score
You can identify a main problem	
They are convincing in their roles	
They are demonstrating variety of relevant issues	
They are working toward to a solution	
The speech was clear with appropriate volume and tone	
The role play captured and maintained audience interest	
You learnt a lot from this role play	

Annex 6.1: Common poisoning drugs, chemicals and house hold products

• Acetaminophen/Paracetamol • Nonsteroidal anti-inflammatory drugs • Antimicrobials • Chloroquine and other aminoquinolines • Anticholinergics • Antidiabetic Agents • Antihistamines • Benzodiazepines • Anticonvulsants • Barbiturates • Carbamazepine • Phenytoin • Cardiac Glycosides • Dextromethorphan • Ethanol • Opiates and Opioids • Phenothiazines and other antipsychotic drugs • Tricyclic Antidepressants	• Caustics and Corrosives • Household products • Detergents • Sodium Hypochlorite (Bleach) • Dettol Hydrogen Peroxide • Carbon Monoxide • Herbal Medicines • Mushrooms • Hydrocarbons • Organophosphates and Carbamates • Herbicides • Rodenticides • Snakebite

Annex 6.2.Antidote recommendations for stocking at health facilities that accept emergency patients (Adapted from Dart et al., 2009 and FMHACA, 2014).

S. No.	Antidote	Poisoning indication
1.	Acetylcysteine injection, 200mg/ml in 10ml ampoule	Acetaminophen
2.	Polyvalent Immune Fab, ovine (Snake Venom Antiserum polyvalent Injection, 10ml)	Snake bite of unknown snake type
3.	Atropine Sulfate Injection, 1mg/ml in 1 ml ampoule	Organophosphorus and N-methyl Carbamates
4.	Calcium chloride *Injection, 10% (100mg/ml)*	Fluoride, Calcium Channel blockers
5.	Calcium gluconate *Injection, 10% in 10ml ampoule*	Fluoride, Calcium Channel blockers, Magnesium sulfate
6.	Calcium disodium EDTA†	Lead
7.	Calcium trisodiumpentetate (CaDTPA)††	Plutonium, Americium or Curium
8.	Cyanide Antidote Kit / Hydroxicobalamine HCl	Cyanide
9.	Deferoxamine mesylate	Iron
10.	Digoxin Immune Fab (Ovine) Digoxin specific, antibody fragments Powder for injection, 40mg	Cardioactive Steroids
11.	Ethanol	Methanol or Ethylene glycol
12.	Flumazenil *Injection, 0.1 mg/ml in 5 ml ampoule*	Benzodiazepine
13.	Glucagon HCl	B-blocker, Calcium channel blockers
14.	Methylene blue	Methemoglobinemia
15.	Naloxone HCl Injection, 0.02mg/ml in 2ml ampoule, 0.4mg/ml in 1ml and 10ml ampoule, 1mg/ml	Opioid and Clonidine
16.	Octeriotide acetate	Sulphonylurea
17.	Physostigmine salicylate Injection, 1mg/ml in 1ml and 2ml ampoule	Anticholinergic syndrome
18.	Pralidoxime chloride Powder for injection, 1g/vial	Organophosphates and N-methyl Carbamate insecticides
19.	Pyridoxine hydrochloride *Injection, 50mg/ml in 2ml ampoule, 150mg/ml*	Isoniazid, Hydrazine
20.	Sodium bicarbonate Injection	Sodium channel blockers
21.	Phytomenadione (Vitamin K inj.)	Warfarin, Rodent poisons
22.	Protamine Sulphate Inj.	Heparin
23.	Sodium Polystyrene Sulphonate Powder	Hyperkalemia

24.	Dextrose 40% injection	Insulin, oral hypoglycemic agents
25.	Thiamine	Alcohol intoxication, alcoholic or starvation ketoacidosis
26.	Trimethoprim, methotrexate,	Leucovorin(Folinic acid)
27.	Caffeine	Propranolol
28.	Penicillamine	Lead, copper, mercury,
29.	Activated charcoal *Powder for reconstitution, 15gm/120ml, 25gm*	Many
30.	Apo morphine Hydrochloride *Injection, 3 mg/ml in 1 ml ampoule*	Parkinsonism

Annex 6.3. Source of Poison Information

Barceloux DG. Medical Toxicology of Drug Abuse; Synthesized Chemicals and PsychoactivePlants. Hoboken: Wiley; 2012.

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Greenberg MI. Editor-In-Chief. Occupational, Industrial and Environmental Toxicology. 2nd ed.Philadelphia: Mosby; 2003.

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White J. A Clinician's Guide to Australian Bites and Stings. Melbourne: CSL Limited; 2013.

Williamson J, Fenner PJ, Burnett JW, Rifkin JF, editors. Venomous & poisonous marine animals. Sydney: University of New South Wales Press; 1996.

Sutherland SK, Tibballs J. Australian Animal Toxins. 2nd ed. Melbourne: Oxford UniversityPress; 2001.

Mc Kenzie R. Australia's Poisonous Plants, Fungi and Cyanobacteria. Collingwood. CSIROPublishing. 2012

Grant WM, Schuman JS. Toxicology of the eye. 4th ed. Springfield: Charles C Thomas; 1993

Murray L, Daly F, Little M, Cadogan M. Toxicology Handbook. 2nd ed. Elsevier Australia.2011

Secondary sources

International Agency For Research On Cancer (IARC) https://www.iarc.fr/

Chemical safety information for intergovernmental organizations http://inchem.org

American Association of Poison Control Centers http://www.aapcc.org/

National Poisons Register. Sydney: Royal Prince Alfred Hospital Toxicology Unit.http://www.npr.org.au

Chemwatch Chemical Database Management System. Melbourne: Chemwatch Pty Ltd.

Chemalert Chemical Database System, Queensland Health Department,

Therapeutic Guidelines (eTG) Toxicology and Wildernesshttp://online.tg.org.au/ip/desktop/index.htm.

MIMS Online or eMIMS. Sydney: MIMS Australia.

AusDI. Canberra: Pharmaceutical Care Information Sources.

Therapeutic Guidelines (eTG) Toxicology and Wildernesshttp://online.tg.org.au/ip/desktop/index.htm

Australian Venom Research Unit (list of exotic antivenoms available in Australia)

http://www.avru.org/reference/reference_avhold.html

Annex 7.1 Food,MedicineandHealthCareAdministrationandControlAuthorityof Ethiopia(FMHACA)AdverseDrugEventreportingform

PatientName (abbreviation | CardNo | Age,Date ofbirth | Sex | Weight | Height

Ethnicgroup---------- Substance ofabuse----------

Information on suspected drug/vaccine S=suspected drug C=concomitantlyused drugs

Drug name(write allinformation includingbrand namebatchno andmanufacturer	S/C route	Dose/dosageform, frequency	Datedrug taking was started (D/M/Y)	Datedrug reaction started (D/M/Y)	Datedrug taking was stopped (D/M/Y)	Indication (Reasonfordrug use)

Adversedrugeventdescription(includeallavailablelaboratorytest results)

_____
_____
_____
_____
_____
_____
_____
_____
_____.

Reactionnecessitated
Discontinuationofdrug/s □YES □No
Hospitalizationprolonged □YES □No

ReactionsubsideafterD/Cofsuspecteddrug
□YES □No □Informationnotavailable
Reactionreappearafterrestartofsuspecteddrug
□YES □No □Informationnotavailable

Treatmentofreaction

Outcome:□Diedduetotheadverseevent □Died,drug maybecontributory □Notyetrecovered
□Recoveredwithoutsequelae □Recoveredwithsequelae □Unknown

Sequelae

Relevantmedicalconditionssuchasallergies,renaldisease,liverdisease,other chronicdiseases,pregnancy etc___

Reportedby:Name Profession: Emailaddress: Telephone
---------- ---------- ---------- ----------

Name ofhealthinstitution Date

Productqualityproblem:Color change,separating ofcomponents,powdering,crumbling,caking,molding, change ofodor,incompletepack,suspectedcontamination,poorpackaging/poorlabeling,etc(Writeif anything differentthangivenabove)				
Drug tradename	BatchNo	Registrationno	Dosageform andstrength	Size/type ofpackage
Forofficeuse only				
Receivedon:			Registrationno:	
Key:D/M/Y;Date/Month/Year D/C;Discontinue treatment Y;YES N;NO				

□□□□□□□□□□□□□ **whatto report**

Allsuspectedreactionstodrugs Unknownorunexpectedreactions Seriousadversedrug reactions
Unexpectedtherapeuticeffects
Allsuspecteddrug interactions Productqualityproblems Treatmentfailures
Medicationerrors

NB.Drugsincludes ***ThisADEreportingform waspreparedbyFMHACAincollaborationwithMSH/SPS and the financialsupportfromUSAID***

Conventionaldrugs
Herbaldrugs
Traditional medicines
Biologicals Medicalsupplies Medicatedcosmetics
□□□□□□□□□□□

□□□□□□□□□□□□□□□□□□□□HQ2

From ---------- BusinessReplyService License NoHQ2

---------- Postageprepaid

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Food,Medicineand HealthcareAdministration and ControlAuthorityof Ethiopia

Food,Medicineand Health CareAdministration and ControlAuthority

Regulatory Information Developmentand Dissemination Team
P.O.Box5681-Tel.0115-523142
AddisAbaba, Ethiopia

Annex 8.1: The Twelve Principles of Ethics for General Public Service

1. ***Integrity***: exhibit the highest standards of professional competence and private conduct
2. ***Loyalty***: dedication to upholding the constitution and the laws and trusted to discharge their duties by fellow public officials.
3. ***Transparency***: to be as open as possible about decisions, taking care to justify actions
4. ***Confidentiality***: not to disclose information of a confidential or private nature
5. ***Honesty***: keep the promises made, be sincere and be free from deceit, fraud or corruption
6. ***Accountability***: be responsible for decisions and actions
7. ***Serving Public Interest***: make decisions and act solely in the public interest and not in private interest
8. ***Exercising Legitimate Authority***: power and authority should be exercised legitimately within the authority of office without any abuse
9. ***Impartiality***: decisions and actions should be made in a fair and equitable manner
10. ***Respecting the Law***: obey the law and comply with enactments, proclamations or directives appropriate for duties and as instructed by relevant authority
11. ***Responsiveness***: listen and respond to the needs of stakeholders timely and with respect and courtesy
12. ***Leadership***: promote and support these principles by taking the lead setting examples

Annex 8.2: Suggested Process of Analysis to Be Used When an Ethical Dilemma Arises

Step I. Identification of Relevant Background Information

The first process step requires identification and evaluation of pertinent background information to ensure that the facts of the specific case are understood. This first step deserves careful consideration and research. Once the facts of a case are known, the moral concerns may be resolved. This step has been divided into three parts: (A) Data gathering, (B) Consideration of the welfare of all affected parties, and (C) Respect for the cultural perspectives of these parties.

Pharmacists already use data gathering when they apply a "systematic approach" to answering any drug information question. When addressing a potential ethical dilemma, the pharmacist must learn about the factual details of the issue, who is directly involved, and whether there is conflict in factual understanding among the involved parties in the issue.

If the matter seems still to involve an ethical dimension once data gathering clarifies the facts, the next step is to consider the rights and responsibilities of all affected parties. The pharmacist, the direct client (patient), other indirect but individual clients (e.g., any existing or unborn children, or spouse), other health professionals (e.g., the patient's physician), other societal groups (e.g., other patients who might be harmed by an incompetent practitioner), and any higher power recognized by the pharmacist have rights and/or responsibilities that should be considered.

Finally, during first consideration of any potential ethical issue, the pharmacist should take into account the cultures of the affected parties. In his reviews of the foundations of modern medical ethics theories.

Step II: Use of Rules and Principles (Action-Guides) to Assist in Analysis of an Ethical Dilemma

If the dilemma persists, once the available background information has been identified and considered, the process of full ethical deliberation should proceed. This second process step of analysis will look at moral rules that may apply to the specific case, as well as at more general pertinent ethical principles. Definitions are provided at the end of this section for a number of ethical rules and principles that are considered particularly relevant to decision-making by pharmacists.

It should be noted that specific action-guides may be considered a rule within one ethical theory and a

principle within another.

Step III: Ethical Theory as a Means to Clarify or Resolve Ethical Dilemmas

This third step of ethical analysis reveals how relevant moral rules and principles interact within the preferred ethical theory to address the given dilemma. When confronted with conflicting ethical rules or principles, the pharmacist may simply resolve the dilemma through his or her moral intuition of "the right thing to do"; even if unconscious, this reflects the individual's at least temporary affiliation to some theory of what constitutes "good versus bad" or "right versus wrong." Sometimes, the professional will find it valuable to more consciously deliberate on how various ethical theories suggest that the relevant rules and principles should be prioritized or balanced.

Annex 9.1: DIS summary and reporting form

_____Hospital Drug Information Service (DIS) **P.O. Box: _____, Telephone: _____, Fax: _____, E-mail: _____**							
Drug Information Query/Response and related activities summary and reporting form							
Name of DI pharmacist:		**Telephone**		**E-mail**			
Data compilation/reporting eriod Date:		**Month:**					
1	**Number of DI requests**			Received:		Replied :	
2	**Number of Requests coming from**	health facility staff:		Staff from other Health faciility:		patient:	
						other	
1	**Requesters' Sex**	Male:		Female:			
2	**Requesters' Qualification/ profession**	Specialist		GP		Health Officer	
		Nurse		Pharmacist		Druggist	
		Student		Other			
II-Background information on query:							
1	**Number of queries received through**:	Walk-in		Phone		Written form	
		E-mail		Fax		Letter	
2	**Type of queries :**	Patient specific:		Academic:		Other/ Not specified	
3	**Classification of Query:**	Therapy		Pregnancy		ADR	
		Interaction		Pharmaceutical		Pharmacology	
		Pharmacokinetics		Administration		Local/Foreign equiv.	
		Availability		Other			
4	**Sources of information used**	Reference books		Journals		In-house database	
		Peer reviewer publication		Internet sites		Package inserts	
		Other DIS		Previous response		Other	
5	**Response communicated by:**	Oral/Verbal		Written/print format		Telephone call	

		E-mail		Notice board		Provide Reference source	
		Provide Literature		Provide Internet source		Other	
6	**Number of requesters who sent feedback**						

B. Additional activities of DIS							
1	**Number of publications issued**	Drug ALERTS		Bulletins		Newsletters	
		Therapy updates		New arrivals/ availability		Other publications	
Continuing Medical Eduction/Patient education (CME/PE) events:							
2	**Number of events organized to:**	The hospital staff		Patients/community		Others	
3	**Number of attendees/ target audiences:**	The hospital staff		Patients/community		Others	
4	**Number of topics related to:**	Drug Specific		Disease specific		Rational use	
		others					
5	**Number of ADR/ADE Reports**	Received from staff		Sent to FMHACA		Feedback received From FMHACA	
6	**DIS' support to DTC** (Formulary management/ Drug use reviews/ studies/ DUE/ Designing strategy)	Facilitate the workshop to conduct DUE on Ceftriaxone					
7	**DIS' support to clinical pharmacy/ pharmaceutical care**	organize educational sessions and meetings with prescribers to sensitize staff on the role of pharmacists in the chronic diseases management					
8	**Major Challenges/ constraints affecting progress**	None					
9	**Actions taken to address challenges/ constraints:**	None					

Report compiled/reported by: _____ Date: _____

Report reviewed by: _____ Date: _____

Seal of the

Health facility/Pharmacy

For Office use only

Report received by: _____ Date: _____ Report sent to home office on: _____

Home/ central office-

Report received on: _____ **Report compiled and documented on:** _____

Annex 10.1: Guideline on how to write a Proposal To Establish and Run a Drug Information Services

I. **Statement of need**

II. **Develop a timeline**

III. **List out the functions and role**

IV. **Get a support from the health facility**

V. **Identify space/office**

VI. **List equipment and resources need**

VII. **Determine personnel to staff to the center**

VII. **Establish communication methods**

VIII. **Determine the target population to serve**

IX. **Determine hours of operation**

X. **Develop a budget (for equipment and drug information resources)**

XI. **Develop Action plan**

Annex 10.2: Work plan for DIS implementation

Work Plan for DIS Implementation

A. General

1. Name of the facility: _____
Address: Region: _____, Town: _____, Telephone: _____, P.O.Box: _____

2. Name of trainee/semail Cell Phone number

1 _____ _____ _____

2_____ _____ _____

A. Information on DIS status

1. Has a DIS been established in the hospital? Yes ☐ No ☐
2. If yes, date of DIS establishment_____
3. If no, reason(s):_____
4. If DIS has been established, are you providing DI service Yes ☐ No ☐
5. If no, reason(s):_____

Objectives/Goals: _____
_____
___

Opportunities regarding DIS: _____
_____

Challenges regarding DIS: _____
_____

C. **Work plan for DIS Implementation (for _____ 1, 2010 to Hamle 30 2010 EC)**

Process Indicator or Milestones	Effective Date	Responsible Person	Collaborators	What resource?	Remark/ Notes
Activity 1:					
Activity 2:					
Activity 3:					
Activity 4:					
Activity 5:					
Activity 6:					

If you plan to have more activities, please use overleaf