Irrational use of medicines is a widespread problem at all levels of health care, but especially in hospitals. This is particularly worrying as resources are generally scarce and prescribers in communities often copy hospital prescribing practices. Use of medicines can be greatly improved and wastage reduced if some simple principles of drug management are followed. But it is difficult to implement these principles because staff from many different disciplines are involved, often with no forum for bringing them together to develop and implement appropriate medicines policies.

A drug and therapeutics committee (DTC) provides such a forum, allowing all the relevant people to work together to improve health care delivery, whether in hospitals or other health facilities. In many developed countries a well functioning DTC has been shown to be very effective in addressing drug use problems. However, in many developing countries DTCs do not exist and in others they do not function optimally, often due to lack of local expertise or a lack of incentives.

Drug and Therapeutics Committees: A Practical Guide provides guidance to doctors, pharmacists, hospital managers and other professionals who may be serving on DTCs and/or who are concerned with how to improve the quality and cost efficiency of therapeutic care. It is relevant for all kinds of DTCs - whether in public or private hospitals and whether at district or tertiary referral level.

This comprehensive manual covers a committee's functions and structure, the medicines formulary process, and how to assess new medicines. The chapters on tools to investigate drug use and strategies to promote rational use are followed by a discussion of antimicrobial resistance and infection control. The publication concludes by explaining in detail how to start a committee or improve the effectiveness of an existing one.

The manual has been developed by the WHO Department of Essential Drugs and Medicines Policy, in collaboration with the Rational Pharmaceutical Management Plus Program of Management Sciences for Health.

DRUG AND THERAPEUTICS COMMITTEES: A PRATICAL GUIDE

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A PRACTICAL GUIDE

WORLD HEALTH ORGANIZATION
In collaboration with:
MSH
MANAGEMENT SCIENCES for HEALTH

WHO/EDM/PAR/2004.1

Drug and therapeutics committees

A practical guide

World Health Organization
Department of Essential Drugs and Medicines Policy
Geneva, Switzerland

In collaboration with
Management Sciences for Health
Center for Pharmaceutical Management
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Contents

Acronyms and abbreviations

ABC	ABC analysis
ADR	adverse drug reaction
AGREE	Appraisal of Guidelines for Research and Evaluation in Europe
AHFS	American Hospital Formulary Service
AMR	antimicrobial resistance
ARR	absolute risk reduction
ASHP	American Society of Health-System Pharmacists
DALYs	disability-adjusted life years
DDD	defined daily dose
DTC	drug and therapeutics committee
DUE	drug use evaluation
DUR	drug utilization review
EDL	essential drugs list
EML	essential medicines list
EDLIZ	Essential Drug List of Zimbabwe
GMP	good manufacturing practices
IM	intramuscular
INN	International Nonproprietary Name
INRUD	International Network for Rational Use of Drugs
IV	intravenous
MCAZ	Medicines Control Authority of Zimbabwe
MI	myocardial infarction
MoH	Ministry of Health
MSH	Management Sciences for Health
MUE	medication use evaluation
NDTPAC	National Drug and Therapeutics Policy Advisory Committee
NNT	numbers needed to treat
QALYs	quality-adjusted life years
RCT	randomized controlled trial
RPM	Rational Pharmaceutical Management Project
RR	relative risk

RRR	relative risk reduction
SC	subcutaneous
SIGN	Scottish Intercollegiate Guidelines Network
SK	streptokinase
STG	standard treatment guideline
TB	tuberculosis
TPA	tissue plasminogen activator
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VEN analysis	vital, essential and non-essential analysis
WHO	World Health Organization

Preface

Inefficient and irrational use of medicines is a widespread problem at all levels of health care (Hogerzeil 1995). Per capita wastage from inefficiencies and irrational use tends to be greatest in hospitals; this is particularly worrisome since resources are scarce and prescribers in communities often copy hospital prescribers. Many of these sources of wastage could be reduced if some simple principles of drug management and use were followed. However, it is difficult to implement these principles because staff from many different disciplines are involved in different aspects of drug management and use. Often there is no forum for these different disciplines to work together in developing and implementing appropriate drug policies.

In hospital settings, a drug and therapeutics committee (DTC) provides a forum to bring together all the relevant people to work jointly to improve health-care delivery. As such, a DTC may be regarded as a tool for promoting more efficient and rational use of medicines. In many developed countries, a well-functioning DTC has been shown to be one of the most effective structures in hospitals able to address drug use problems (Weekes and Brookes 1996). However, in many developing countries DTCs do not exist and in others they do not function effectively.

A DTC involves its members in a great deal of work. It may be easy to identify members, roles and functions for a DTC, but it is much more difficult to develop and implement strategies to change medicine use practices. DTCs will not, therefore, work unless the staff involved are motivated and prepared to make the effort. A DTC can only work in health systems where there are:

- sufficient staff who understand and are able to undertake the necessary work
- incentives (for example recognition, allocated work time for DTC activities) for the professional staff involved
- accountability of the hospital and its staff for the money they spend on medicines and the quality of care that they provide.

This manual aims to provide practical guidance to doctors, pharmacists, hospital managers and other professionals who may be serving on DTCs, or who are concerned with how to improve the quality and cost efficiency of care. The manual covers:

- general principles, strategies and activities that can be adopted to improve the quality and cost efficiency of care
- what the roles and responsibilities of a DTC should be and how these may be achieved.

The guidance provided in this manual is aimed at all kinds of DTC – whether in public or private hospitals and at all levels, from district level to tertiary referral level. Since health systems in different countries vary widely, not all the information included in this manual will be relevant for all DTCs. Where certain information is only relevant to higher levels of health care, this has been indicated in the text.

This manual has been developed by the Department of Essential Drugs and Medicines Policy, WHO, Geneva, in collaboration with the USAID-funded Rational Pharmaceutical

Management Plus Programme of Management Sciences for Health, Boston, USA. The draft was developed in a participatory way, building on the course materials used in international training courses on DTCs and on experiences gained from pilot projects conducted in Zimbabwe and Indonesia.

The words 'drugs' and 'medicines' are used interchangeably in the text.

We would be very happy to receive comments, which may be sent to:

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1. Introduction

Summary

Inappropriate use of medicines wastes resources and seriously undermines the quality of patient care. A drug and therapeutics committee (DTC) can significantly improve drug use and reduce costs in hospitals and other health care facilities in the following ways:

- providing advice on all aspects of drug management
- developing drug policies
- evaluating and selecting drugs for the formulary list
- developing (or adapting) and implementing standard treatment guidelines
- assessing drug use to identify problems
- conducting interventions to improve drug use
- managing adverse drug reactions and medication errors
- informing all staff members about drug use issues, policies and decisions.

1.1 Why are drug and therapeutics committees needed?

Essential medicines are one of the most cost-effective ways of saving lives and improving health, and constitute 20–40% of health budgets in many developing countries. Increasing costs and lack of resources often result in public health systems being unable to procure sufficient medicines to meet patient demand. Despite this, medicines are often managed and used inefficiently and irrationally. This may be due to many factors, for example inadequate training of health staff, lack of continuing education and supervision, or lack of updated, reliable, unbiased drug information. Particular areas of inefficiency and drug use problems include:

- poor selection of medicines, without consideration for relative efficacy, cost-effectiveness or local availability
- inefficient procurement practices, resulting in non-availability, inadequate quality, wastage, or use of unecessarily expensive medicines
- prescribing not in accordance with standard treatment protocols
- poor dispensing practices resulting in medication errors, and patients' lack of knowledge about dosing schedules
- patients not adhering to dosing schedules and treatment advice.

Inefficient use of medicines affects the safety and quality of therapeutic care and wastes resources. According to WHO (1985):

> Rational drug use requires that the patients receive drugs appropriate to their clinical needs in doses that meet their individual requirements (right dose, right intervals and right duration). These drugs must be of acceptable quality, and available and affordable, at the lowest cost to patients and the community.

When the use of medicines is not in accordance with this definition, there are often undesirable health and/or economic outcomes. Such outcomes include insufficient therapeutic effect, adverse drug reactions, preventable side-effects and interactions from medicines, and increasing resistance of bacterial pathogens to antimicrobial medicines; these may all result in increased or prolonged hospital admissions, which are expensive.

Some inefficiencies result from lack of an effective forum that brings together pharmacists, clinicians and administrators to balance the demand for quality care with financial constraints. There may be tension between prescribers and financial managers about which medicines should be available for what problems. DTCs are a forum to bring together all stakeholders involved in decisions about drug use; they may exist at any level within the health-care system – at district level (overseeing primary health-care facilities), in hospitals, or at the national level. In developed countries hospital DTCs have been shown to be very effective in safeguarding and promoting efficient and rational use of medicines (Crawford and Santell 1994, Weekes and Brookes 1996) by, for example:

- establishing documented rules and policies for all aspects of drug management including the selection of formulary list medicines and agreement of treatment protocols
- conducting continuing education, audit and feedback, drug utilization review and monitoring of adverse drug reactions and medication errors.

1.2 Goals and objectives of the DTC

The goal of a DTC is to ensure that patients are provided with the best possible cost-effective and quality of care through determining what medicines will be available, at what cost, and how they will be used.

In order to achieve this goal a DTC will have the following objectives:

- to develop and implement an efficient and cost-effective formulary system which includes consistent standard treatment protocols, a formulary list and formulary manual
- to ensure that only efficacious, safe, cost-effective and good quality medicines are used
- to ensure the best possible drug safety through monitoring, evaluating and thereby preventing, as far as possible, adverse drug reactions (ADRs) and medication errors
- to develop and implement interventions to improve medicine use by prescribers, dispensers and patients; this will require the investigation and monitoring of medicine use.

1.3 Functions of the DTC

There are many possible functions of a DTC, and the committee must decide which to undertake as a priority; this decision may depend on local capacities and structure. Furthermore, certain functions will require liaison with other committees or teams, for example the infection control committee or the procurement team. The most important DTC functions are summarized below.

1.3.1 Advisory committee to medical staff, administration and pharmacy

The DTC is a valuable resource that can **provide advice** to medical staff, nurses, administration, pharmacy and other departments and groups within the hospital. The DTC can advise on all issues, policies and guidelines concerning the selection, distribution and

use of medicines. Usually a DTC will provide advice and an executive body, usually the pharmacy or hospital management, will implement it.

1.3.2 Development of drug policies

The DTC is the most appropriate body to **develop drug policies** within a hospital or group of health facilities, since the committee members will have the most experience and training in drug therapy and supply. Policies and procedures are the primary activity within a DTC, since they provide the foundation for other recommendations that may later arise from the DTC. Drug policies may vary in different hospitals and countries, but all hospitals should have specific policies concerning:

- criteria for inclusion of medicines on the formulary list (essential medicines list (EML))
- standard treatment guidelines and treatment algorithms, which should be the basis of formulary selection
- periodic use of medicines not on the formulary list, for example restricting their use to specified prescribers on a named patient basis only, or only allowing 10% of the hospital medicines budget to be spent on them
- expensive or dangerous medicines, such as third-generation antibiotics or oncological drugs, which are restricted to certain practitioners, departments or patients (structured order forms may be used to implement this policy)
- drugs that are under investigation for safety or efficacy
- generic substitution and therapeutic interchange
- drug representatives and promotional literature.

1.3.3 Evaluating and selecting medicines for the formulary list

Perhaps the most important function of a DTC is the evaluation and selection of medicines for the essential medicines list or formulary list. Drugs should be selected on the basis of the standard treatment guidelines or protocols that have been developed or adapted for use in the hospital or health facilities. The evaluation of medicines requires significant expertise and time commitment and a rigorous, transparent approach. Documented evidence for the efficacy, safety, quality and cost of all drugs under consideration for inclusion in the formulary list must be examined. Periodic review is necessary because of changing costs and indications, new information on safety, and the emergence of new medicines. The documents reviewed will depend upon the expertise of the committee and may include reputable textbooks, published treatment guidelines and formularies, newsletters and primary drug literature. See section 3.2 and chapter 4 for more information on selection and evaluation of medicines.

1.3.4 Developing standard treatment guidelines

Standard treatment guidelines (STGs) or protocols are a proven way to promote rational use of medicines provided they are:

- developed in a participatory way involving end-users
- easy to read and up to date
- introduced with an official launch, training, supervision and wide dissemination (Grimshaw and Russell 1993, Woolf et al. 1999).

Furthermore, STGs provide a benchmark of optimum treatment in the monitoring and audit of drug use. A DTC should either develop STGs from scratch or adapt them from elsewhere for use in their own hospital. Development of STGs from scratch will result in greater local ownership and acceptance, but is difficult and will consume time and resources. Adaptation or adoption of STGs from elsewhere is much easier and quicker, but will result in less local ownership and acceptance. See section 3.4 for more information on treatment guidelines.

1.3.5 Assessing medicine use to identify problems

Appropriate changes within the formulary list or other interventions may correct a number of problems in how medicines are used. It is important for the DTC to identify the priority problems and make appropriate recommendations. Appropriate methods to identify drug use problems include:

- aggregate drug consumption data review including ABC and VEN analysis and use of defined daily dose (DDD) methodology (see section 6.1)
- monitoring indicators of medicine use, including adherence to standard treatment guidelines (see section 6.2)
- drug use evaluation (DUE), also known as drug utilization review (see section 6.4)
- monitoring adverse drug reactions and medication errors (see chapter 5)
- antimicrobial resistance surveillance (see section 8.1).

1.3.6 Conducting effective interventions to improve medicine use

There is no point in a DTC collecting information on drug use problems if nothing is done to correct the problems identified. The DTC is the main body within a hospital, or group of health facilities, responsible for ensuring that drug information is provided to health staff and also for conducting interventions to promote more rational drug use. Monitoring and supervision, audit and feedback, educational programmes, in-service training, use of standard treatment guidelines, provision of unbiased drug information, prescribing restrictions and automatic stop orders are some important interventions. See chapter 7 on strategies to promote the rational use of medicines.

1.3.7 Managing adverse drug reactions

Adverse drug reactions (ADRs) are serious in terms of patient harm (morbidity and mortality) and avoidable economic costs. One large meta-analysis estimated that ADRs cause 3–4% of all hospital admissions in the USA and that in 1994 the incidence of ADRs was 6.7% (2.2 million events) with 106 000 fatalities (Lazarou et al. 1998). These estimates should be viewed with caution because of the heterogeneity among studies and small biases in the sample, but the data nevertheless suggest that ADRs are a large and serious problem. Adverse drug reactions may be due to the unknown effects of new (or older) drugs, unknown drug combinations and interactions, or poor drug quality. DTCs are responsible for ensuring that patients are treated as safely as possible. Monitoring and minimizing adverse drug reactions is an essential part of this function (see section 5.3).

1.3.8 Managing medication errors

Medication errors occur in all health-care settings, no matter how good the health-care staff are at prescribing, dispensing and administering medicines. Even if there is no error on the part of health-care staff, patients may take drugs incorrectly. Causes are numerous and include lack of knowledge, tiredness of staff, careless work attitudes, poor procedures,

lack of policies, unfamiliar dosage forms and human error. DTCs can reduce such errors by monitoring, analysing, reporting errors and implementing corrective action (see section 5.1).

1.3.9 Information dissemination and transparency

The DTC must disseminate information about its activities, decisions and recommendations to the staff who must implement the DTC's decisions. This may seem obvious, but it is often forgotten. Inadequate dissemination of information leads to a loss of credibility. It is also very important that the DTC operates in such a way as to ensure transparency of all its decisions and to avoid conflict of interest. In particular, members should either have no relationship with pharmaceutical companies or declare it openly so that conflicts of interest can be avoided. The only acceptable contact with pharmaceutical companies is to ensure the flow of information about their drug products in a way that is as unbiased as possible (see sections 2.1 and 7.4.2).

1.4 Role of the DTC in the drug management cycle

The drug management cycle (Figure 1.1) illustrates the necessity for coordination of managerial and technical support with appropriate drug policies and guidelines, in order for any drug system to run smoothly (MSH 1997, part IV, section A on 'Organization and Management'). The figure highlights the coordination between the DTC and the drug purchasing and inventory control body.

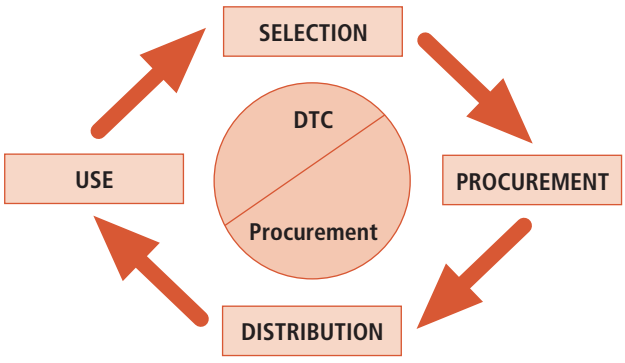


Figure 1.1 **The drug management cycle**

The DTC will often have to coordinate with those responsible for procurement and distribution of medicines. The DTC would not normally do the procurement itself: its role would normally be to ensure that the formulary system and other drug policies developed by the DTC are implemented by the procurement department. Every effort should be made to avoid the DTC degenerating into a forum only for making procurement decisions and complaining to the pharmacist about stock-outs. Furthermore, it is unwise to concentrate too much power over the pharmaceutical system in any one body, as this may lead to corrupt practices. The functions of selecting medicines, procurement, payments and inventory control are best kept separate (WHO/UNICEF/UNFPA/WB 1999).

2. Structure and organization of a drug and therapeutics committee

Summary

In order for a DTC to function it should have a multidisciplinary, transparent approach, technical competence and an official mandate. It is essential to define and document:

- the membership of the DTC, including the chairperson and secretary, and criteria for membership
- the goals, objectives and functions of the DTC
- how the DTC will operate and its terms of reference
- the funding sources identified
- the mandate – DTCs will not work without senior administrative support
- the relationship of the DTC with other subcommittees for specific areas of work
- a process for self-assessment and evaluation.

2.1 Principles in setting up a DTC

It may be easy to establish a DTC, with a list of core and additional members, all with different expertise, objectives and functions, but it may be very difficult to ensure that it functions effectively. Success will depend on having strong and visible support from the senior hospital management and abiding by the principles listed below.

2.1.1 A multidisciplinary approach sensitive to local politics

DTC activities will involve different cadres of health professional, who will have different experiences, beliefs, skills, practices, motivations and status. Often a DTC must manage conflict arising between clinicians and the pharmacy or administration concerning prescribing restrictions that result from the implementation of agreed guidelines. Such conflicts can be reduced if staff are convinced of the need for, and benefits of, change and there is strong institutional commitment with the support of people in authority. Wide representation on the DTC and documenting and disseminating decisions taken to correct problems in the use of medicines helps to convince health-care workers. Everyone who contributes should be acknowledged.

2.1.2 Transparency and commitment to good service

The success of a DTC will depend upon its being active, working regularly in a consistent direction and making sound decisions in a transparent way. This is especially important in medicine selection and procurement policies. The people involved should not be influenced by inappropriate drug advertisements, promotional activities or personal financial interests. All committee members should be required to sign a 'declaration of interest' (see annex 2.1). Such a declaration can bind members to the working principles and ethics of the DTC, and to their roles and responsibilities to other health-care staff, the hospital management and the community.

2.1.3 Technical competency

A DTC must have the appropriate technical competence. Members will have different competencies and the DTC process of discussion and appraisal of drug use issues is a good way to educate members in areas outside their expertise. Good science and evidence (if possible) must be the basis of all DTC decisions.

2.1.4 Administrative support

Administrative support is very important, as otherwise a DTC may not be able to implement its decisions. Administrative support can provide the executive authority needed to gain the cooperation of senior medical staff. The administration can also provided the funds needed to undertake many of the DTC's activities.

2.2 Steps in setting up and managing the DTC

The most effective way of gaining support is through a dynamic DTC that can formulate policy and guidelines with consensus of all parties and that is seen to be sensitive to comments.

STEP 1 Organizing the committee and selecting members

Opinions vary regarding the optimal size and composition of the committee. Smaller committees may be appropriate for smaller hospitals; larger ones may be useful in big hospitals with wider work perspectives. Fewer members may allow consensus agreements to be reached more easily. More members can provide greater expertise, reduce the workload for individual members, and increase the ease of implementation of decisions. All committees should have sufficient members to represent all stakeholders, including the major clinical departments, the administration and the pharmacy.

Members should be selected with reference to their positions and responsibilities and they should have defined terms of reference. In most hospitals, the membership includes:

- a representative clinician from each major specialty, including surgery, obstetrics and gynaecology, internal medicine, paediatrics, infectious diseases, and general practice (to represent the community)
- a clinical pharmacologist, if available
- a nurse, usually the senior infection control nurse, or sometimes the matron
- a pharmacist (usually the chief or deputy chief pharmacist), or a pharmacy technician where there is no pharmacist
- an administrator, representing the hospital administration and finance department
- a clinical microbiologist, or a laboratory technician where there is no microbiologist
- a member of the hospital records department.

Other members may also be included for their particular expertise, for example a drug information specialist, quality assurance specialist or consumer group representative. In Australia consumer representatives have included a retired judge, a psychiatric patient, a member of a pensioners' association and a volunteer hospital worker. However, with regard to consumer representatives, "beware the politician with a hidden agenda".

A dedicated and committed **chairperson** and **secretary** are critical to the success and efficiency of a DTC. In most hospitals, a senior medical doctor, ideally well-known and respected, is appointed as the chair and the chief pharmacist as the secretary. The chair and secretary should be allotted sufficient time for their DTC functions, and this should be

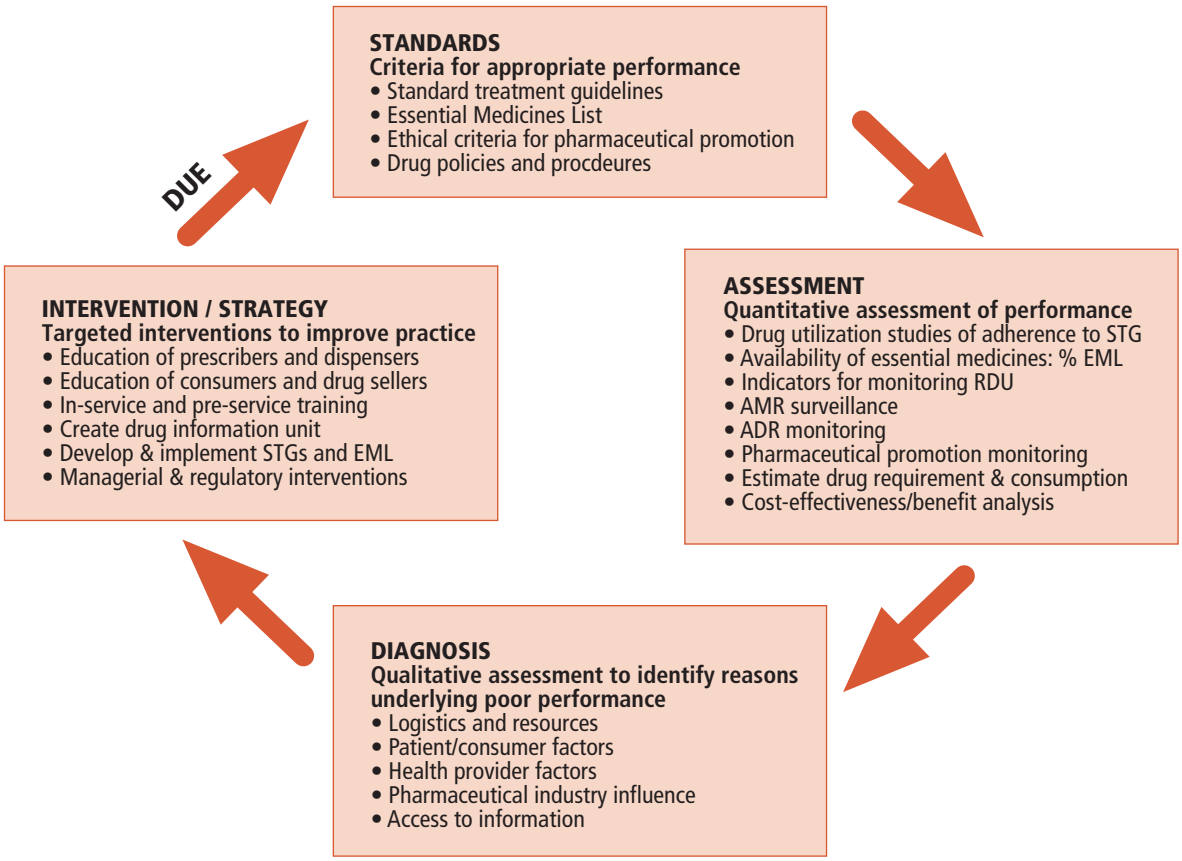
included in their job descriptions and terms of reference. The allotted time should be sufficient to cover all DTC meetings and other work in relation to the meetings. Non-member specialists can be invited during discussions of important issues. In large hospitals, various subcommittees can be established to address particular issues, for example antibiotic use, adverse drug reactions, medication errors and drug use evaluation/audit. All hospitals should have an infection control committee; if such a committee does not exist, the DTC should establish it. Where other committees exist, the DTC should liaise and coordinate with them in order to avoid duplication of activities.

STEP 2 Determine the objectives and functions of the committee

It is not possible for a DTC to do everything. The first thing a DTC should do is to agree its terms of reference, which specify the DTC's place in the organizational structure of the hospital, its goals, objectives, scope of authority, functions and responsibilities. The most important objectives and roles have already been described in chapter 1. Once basic functions, such as a formulary system, are implemented, the DTC can move on to other activities. Annex 2.2 shows the terms of reference of the DTC in a Zimbabwean hospital. Sometimes the initial functions of the DTC, during the time of organization, depend on the prevailing clinical and pharmaceutical management problems that must be immediately addressed. This is a good way of getting the support of the management and the agreement of medical personnel.

Figure 2.1 shows how the different possible functions of a DTC interrelate. The DTC is responsible for maintaining standards. In order to do this, the DTC must define standards,

Figure 2.1 **The DTC's cycle of activities and function**



assess performance, diagnose why performance is poor and introduce measures to improve it.

STEP 3 Determining how the committee will operate

- **Regular meetings of the DTC**, at least quarterly and preferably monthly, are important. The schedule may vary depending on needs. Special meetings can be convened when necessary. The length of meetings should be limited, as clinician members of the committee are unlikely to attend or to stay throughout if the meetings are too long.
- **Regular attendance** of members at committee meetings is often a problem. As a solution, some institutions make it a part of the requirements for reappointment. Other institutions provide some monetary incentives, or serve food or refreshment at meetings.
- **The agenda, supplementary materials and minutes of the previous meeting** should be prepared by the secretary and distributed to the members for review in sufficient time before the meeting. These documents should be kept as permanent records of the hospital and should be circulated to chairpersons/directors of all clinical departments.
- **All DTC recommendations should be disseminated** to the medical staff and other concerned parties and authorities in the hospital. Regular hospital activities such as grand ward rounds and clinical discussions can be used as venues to discuss recommendations and to educate the health staff on the proposed policies for implementation.
- **All DTC operating guidelines, policies and decisions should be documented**. This documentation should include the decisions on actions to be taken if the decisions, guidelines or policies are not followed. Relevant documentation must be made available to interested parties such as staff members and drug companies. Members of the committee should be responsible for disseminating the resolutions of the DTC.
- **Liaison of the DTC with other hospital committees** and regional or national committees is important, for two reasons:
  - — to harmonize related activities (for example, surveillance of antimicrobial resistance (AMR) and antimicrobial use)
  - — to share information concerning common activities (for example, monitoring of adverse drug reactions and educational strategies such as continuing medical education).

STEP 4 Seeking a mandate

Only with a mandate from the most senior authority in the hospital is a DTC credible and sustainable. The mandate of a DTC should specify:

- its roles and functions
- its place in the organizational structure
- its membership
- its scope and lines of authority.

The strongest mandate a DTC can have is that issued by the government, as in Zimbabwe (see annex 2.3). In some industrialized countries, hospitals are required to have DTCs in order to be accredited by professional societies and universities as training institutions. In other countries patients can only get reimbursement for treatment from hospitals that are accredited by the insurance companies and such accreditation may require functioning DTCs.

STEP 5 Identifying budgetary sources

The DTC must be able to identify budget resources to support its own activities (such as meetings or incentives for its members) and those activities it recommends for implementation (for example, educational programmes, development of standard treatment protocols, drug utilization review and supervision). Budgeted staff time should also be reflected in their job descriptions. Usually the budget requirement is not substantial and can be justified to the hospital administration on the basis of drug cost savings that can be realized through the DTC activities. The DTC should be able to demonstrate its own cost-effectiveness when requesting a regular budget allocation from the hospital management. To this end, the DTC should prepare an annual action plan with corresponding budget requirements. It is more convincing to present budgetary requirements together with past or potential future cost savings.

STEP 6 Forming subcommittees to address specific issues

Often there are specific areas which need a great deal of extra work and expertise that the DTC cannot provide or give time to, for example, the use of antimicrobials. Many DTCs have dealt with this issue by forming a subcommittee to work in the specified field on behalf of the DTC and report back. See chapter 8 on antimicrobials and injections.

BOX 2.1 INDICATORS TO ASSESS DTC PERFORMANCE AND IMPACT

- Is there a DTC document that indicates its terms of reference, including its goals, objectives, functions and membership?
- Is the DTC in the organizational chart of the hospital?
- Is a budget allotted to DTC functions?
- Does the DTC have established criteria and authority concerning drug selection?
  - How many medicines are there in the hospital formulary?
  - Are there documented criteria for addition to and deletion from the list and requests for the use of non-formulary medicines?
  - What percentage of prescribed medicines belong to the hospital formulary?
- Has the DTC been active in the development and implementation of STGs?
  - Has the hospital developed/adopted its own STGs?
  - Have drug utilization studies been performed to assess adherence to STGs?
- Has the DTC organized educational activities about medicines?
  - Have there been any organized training and lectures for health-care staff?
  - Is there an established library accessible to staff?
  - Is there continuing medical education?
  - Is there a drug information service available to staff?
- Have any intervention studies to improve medicine use been undertaken?
- Has the DTC been involved in drug budget allocation?
  - Was the DTC consulted during drug budget allocation?
  - Was DTC clearance needed prior to drug budget approval?
- Has the DTC developed a policy for controlling the access of drug representatives and promotional literature to hospital staff?

STEP 7 Assessment of the DTC's performance

Self-assessment and evaluation of the DTC are very important if performance and impact are to be improved. The organizational development and performance of the DTC should be monitored continuously and documented, especially if the DTC expects the hospital management to provide continuing funds. Some indicators that can be used in DTC self-assessment are shown in box 2.1. These indicators are considered to be core parameters that should be used. However, the DTC can develop other indicators and measures that will suit its purpose. Most important is for the indicators to be used in evaluating the impact of the DTC. In this way, the DTC may see if it is achieving its goals and objectives and justify the continued support of the hospital management.

ANNEX 2.1

Example of a declaration of interest form

DECLARATION OF INTEREST FORM

Name ..... Position .....

Have you, or anyone in your family, any financial or other interest in any pharmaceutical manufacturer or supplier, and which may constitute a real, potential or apparent conflict of interest?

Please tick: ☐ Yes ☐ No

Have you had, during the past 4 years, any employment or other professional relationship with any organization that is a pharmaceutical manufacturer or supplier or represents such organizations?

Please tick: ☐ Yes ☐ No

If you answered 'yes' to either question, please give details in the box below.

Type of interest, for example patents, shares, employment, association, payment*	Name of commercial entity	Belongs to you, your family or work unit?	Current interest? or year that interest ceased

* Amounts do not have to be declared

Is there anything else that could affect, or be perceived to affect, your objectivity or independence in carrying out your duties in the DTC?

I hereby declare that the disclosed information is correct and that no other situation of real, potential, or apparent conflict of interest is known to me. I undertake to inform you of any change in these circumstances.

Signature ..... Date .....

Types of financial or other interests

- Any payment for performance of work or research or educational grants during the past four years by any commercial entity that has an interest in the DTC's work.
- Current proprietary interest in a substance, technology or process (for example ownership of a patent), being considered by the DTC or otherwise related to the DTC's work.
- Current financial interest (for example shares, bonds) in a commercial entity with an interest in the DTC's meetings or work. Share holdings through general mutual funds etc., where the person has no control over the selection of shares, are exempt.
- Any employment, consultancy, directorship, or other position during the past 4 years or presently under negotiation, whether paid or not, in any commercial entity (for example a pharmaceutical company) that has an interest in the DTC's work.

ANNEX 2.2

Model terms of reference for a DTC in Zimbabwe

Name: Hospital Drug and Therapeutics Committee of ..... Hospital.

Status: The DTC is a standing hospital committee responsible, through its chairman, to the hospital executive.

Chairman: The hospital executive shall appoint the Medical Superintendent or a senior doctor to chair the committee.

Secretary: The committee secretary will usually be the pharmacist. In hospitals without a pharmacist, the hospital executive can appoint the pharmacy technician or any other member of the committee to be secretary.

Members: The hospital executive appoints the other committee members on a representational basis and also to take advantage of the available human resources in the hospital and community.

Goals:

- Improved health and economic outcomes of hospital care, particularly those related to drug use.
- Rational and cost-effective drug use through collaborative drug management involving all health workers.

Objectives:

The committee will be responsible for defining its own specific objectives on an annual basis. Each committee can do that by reviewing the following objectives and choosing what they want to work on.

1. To formulate and implement policies for selection and use of drugs:
   — to develop and manage a hospital essential drugs list
   — to develop and implement standard treatment guidelines
   — to carry out drug utilization reviews in the hospital
   — to provide prescribers with objective drug information
   — to monitor and analyse expenditure on drugs.
2. To carry out educational and other activities aimed at improving prescribing and dispensing practices in the hospital.
3. To monitor and report adverse drug reactions to the Medicines Control Authority of Zimbabwe (MCAZ).
4. To monitor medication errors and act to prevent their recurrence.
5. To regulate operations of the pharmaceutical industry in the hospital.

ANNEX 2.3

Example of a mandate for a DTC: excerpts from the Zimbabwe National Drug Policy 1998

- The Ministry of Health (MoH) will formally establish the National Drug and Therapeutics Policy Advisory Committee (NDTPAC) by providing appropriate terms of reference and a working budget. The NDTPAC will be composed of experts in all the medical and pharmaceutical fields, representing different levels of the health-care system.
- The MoH recognizes the need for Drug and Therapeutic Committees (DTCs) in order to promote the rational use of drugs in the health-care institutions.
- The MoH will ensure that DTCs are established in district, provincial and central hospitals, local authorities and private institutions. The committees will be composed of senior staff, pharmacy personnel, doctors, nurses, laboratory staff and co-opted members when indicated.
- The MoH will issue guidelines for the formation and functioning of these committees and the NDTPAC will coordinate and advise on the work of the committees.
- The committees will, among other duties, be responsible for determining the range, number and quantity of the Essential Drug List of Zimbabwe (EDLIZ) drugs to be available in the health facility, guiding all health workers in the rational use of drugs and use of the EDLIZ standard treatment guidelines (STGs).
- The committees will make hospital formularies and monitor drug use. The MoH through the Directorate of Pharmacy Services will monitor and evaluate their activities.

3. Managing the formulary process

Summary

The formulary process is critical to good health care and consists of developing and implementing:

- a formulary list (essential medicines list) consisting of the most cost-effective, safe, locally available drugs of assured quality that will satisfy the health care needs of the majority of the patients
- a formulary manual containing summary information on medicines
- standard treatment guidelines containing essential information on how to manage common diseases.

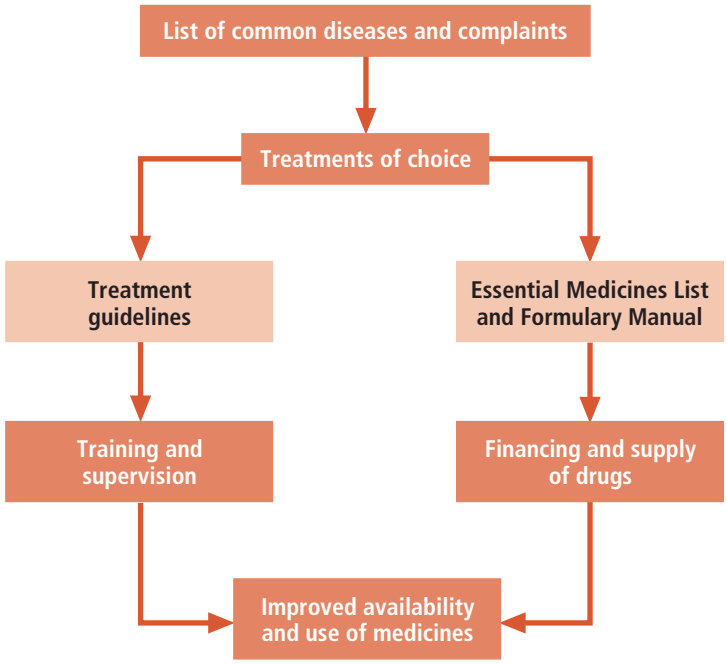
A formulary list and formulary manual should be developed and maintained based on recommended treatments from standard treatment guidelines, using explicit drug selection criteria, that have been agreed previously by all departments. Standard treatment guidelines can be adopted or adapted from elsewhere, which is less work, or developed from scratch, which involves a great deal of work but may result in more acceptability and use due to a sense of ownership. Critical to future use by health workers is their involvement in the development and updating process, the quality of the content, a user-friendly format, adequate distribution and follow-up supervision.

3.1 The formulary process

The formulary process is the cornerstone of good pharmaceutical management and rational drug use. It consists of preparing, using and updating a formulary list (essential medicines list, EML, or essential drugs list, EDL), a formulary manual (providing information on drugs in the formulary list) and standard treatment guidelines (STGs). Choosing the most appropriate therapies and selecting the most cost-effective good-quality drugs leads to better quality of care and more efficient, equitable use of resources.

Strict adherence to a formulary list alone will not improve treatment practice if drug selection is not based on STGs (i.e. if there is no consistency between the formulary list and the STGs). Furthermore, essential medicines can also be used inappropriately if there are no guidelines for disease management. Ideally, a formulary list should be developed after the appropriate treatment guidelines for common diseases have been identified or developed. In many countries, there are already national STGs and other texts on standard treatment protocols that can be followed and used as a starting point when developing a hospital formulary list or local STGs. Once a formulary list is established, a formulary manual, containing information on all the medicines in the formulary list, can be developed. Figure 3.1 shows the relationship between STGs and EMLs and how these affect respectively the use and the availability of medicines.

Figure 3.1 **How STGs and EMLs lead to better prevention and care**



3.2 The formulary list (essential medicines list)

> Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence, evidence of efficacy, safety and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility (WHO 2002a).

It is difficult to achieve efficiency in the hospital pharmaceutical system if there are too many medicines. All aspects of drug management, including procurement, storage, distribution and use, are easier if fewer items must be dealt with. Appropriate selection of drugs can achieve the following results:

- **Cost containment and enhanced equity in access to essential medicines**: Procuring fewer items in larger quantities results in more price competition and economies of scale with regard to quality assurance, procurement, storage and distribution. Such economies can lead to improved drug availability at lower costs, so benefiting those who are in most need.
- **Improved quality of care**: Patients will be treated with fewer but more cost-effective medicines for which information can be better provided and prescribers better trained. Prescribers gain more experience with fewer drugs and recognize drug interactions and adverse reactions better. Quality of care will be further improved if medicine selection is based on evidence-based treatment guidelines.

3.2.1 Criteria in medicine selection

Which drugs are selected depends on many factors, such as the pattern of prevalent diseases, the treatment facilities, the training and experience of available personnel, the financial resources, and genetic, demographic and environmental factors. WHO (1999) has developed the following selection criteria:

- Only those medicines should be selected for which sound and adequate data on efficacy and safety are available from clinical studies, and for which evidence of performance in general use in a variety of medical settings has been obtained.
- Each selected medicine must be available in a form in which adequate quality, including bioavailability, can be assured; its stability under the anticipated conditions of storage and use must be established.
- When two or more medicines appear to be similar in the above respects, the choice between them should be made on the basis of a careful evaluation of their relative efficacy, safety, quality, price and availability.
- In cost comparison between medicines, the cost of the total treatment, and not only the unit cost of the medicine, must be considered. Where drugs are not entirely similar, selection should be made on the basis of a cost-effectiveness analysis.
- In some cases, the choice may also be influenced by other factors, such as pharmacokinetic properties, or by local considerations such as the availability of facilities for storage or manufacturers.
- Most essential medicines should be formulated as single compounds. Fixed-ratio combination products are acceptable only when the dosage of each ingredient meets the requirements of a defined population and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance.
- Drugs are specified by the international nonproprietary name (INN) or generic name without reference to brand names or specific manufacturers.

All DTCs should agree an explicit set of criteria, based upon the WHO criteria, for selecting medicines, so that the selection process can be objective and evidence-based. Without an evidence-based approach, decisions may be taken according to the doctors who 'shout loudest', and it may be difficult to persuade other prescribers to abide by the list. The criteria for drug selection and the procedure for proposing a drug to be added to the formulary list should be published (see section 3.2.3). Not all evidence is equally strong. For example, randomized controlled trials are less subject to bias than expert opinion and are therefore thought to constitute a higher level of evidence. The level of evidence should be acknowledged when publishing selection criteria and decisions. One classification scheme for levels of evidence is that used by the Scottish Intercollegiate Guideline Network (SIGN), as shown in Table 3.1.

3.2.2 Developing and implementing a formulary list

The hospital formulary list should be consistent with the national essential medicines list (EML), if the latter is available. It is very important that an explicit and previously agreed process and selection criteria be followed at each step in order to increase prescriber confidence in the validity and usefulness of the list.

Table 3.1 **SIGN levels of evidence**

1++	**High-quality** meta analyses; systematic reviews of randomized controlled trials (RCTs); or RCTs with a **very low risk of bias**
1+	**Well conducted** meta analyses; systematic reviews of RCTs; or RCTs with a **low risk of bias**
1–	Meta analyses; systematic reviews of RCTs; or RCTs with a **high risk of bias**
2++	**High quality** systematic reviews of case-control or cohort studies; or high quality case-control or cohort studies with a **very low** risk of confounding, bias, or chance and a **high probability** that the relationship is causal.
2+	Well conducted case-control or cohort studies with a **low risk** of confounding, bias, or chance and a **moderate probability** that the relationship is causal
2–	Case-control or cohort studies with a **high risk** of confounding, bias, or chance and a **significant risk** that the relationship is not causal
3	Non-analytic studies, e.g. case reports
4	Expert opinion.

STEP 1 Prioritize a list of common problems/diseases being treated in the hospital and determine the first choice of treatment for each problem

The diseases may be ranked to identify the most common diseases being treated in the hospital by consulting all medical departments and reviewing the previous hospital mortality and morbidity records. For each disease, an appropriate first-choice of treatment should be identified using STGs – either nationally or locally developed. If there are no published STGs endorsed by the health ministry, publications by WHO, unbiased professional organizations and academia can be used. Alternatively, an expert committee can be brought together to identify the appropriate treatment for each of the common health problems. A commonly used alternative method of developing a formulary list – easier, but not recommended – consists of reviewing the existing formulary list of the hospital concerned or any other hospitals in the country. In such circumstances, the *WHO model list of essential medicines* (WHO 2002a) may also be used as a starting point. The capability of the hospital and its staff to handle specific drugs should not be forgotten during the selection process. For example, warfarin is not suitable for use unless the hospital has a facility to monitor prothrombin time (blood clotting time).

STEP 2 Draft, circulate for comment, and finalize the formulary list

A draft of the list must be prepared. It is useful to identify:

- the most important medicines (which are absolutely essential) and those that are less essential
- the most expensive medicines
- whether all the medicines that are prescribed in large volumes, or are expensive, are essential (see ABC analysis and VEN analysis in chapter 6).

Each department, whether clinical or involved in non-clinical drug management, must be given the chance to comment on the list. The DTC must deliberate on their comments and provide feedback. All information to be discussed and deliberated upon, such as disease profile and STGs, must be available during the discussions, together with evidence-based reviews where possible. Finally, the DTC must agree and disseminate the formulary list and the reasons for its choices.

STEP 3 Develop policies and guidelines for implementation

The formulary list will never be useful unless there are documented policies and guidelines on how it should be used. These should include:

- who should use the list (prescribers and the procurement department should both abide by the list)
- how the list should be reviewed and updated
- a clear mechanism for adding and deleting medicines from the list (section 3.2.3)
- how medical staff can request medicines that are not included on the list in exceptional or emergency situations (for example, certain non-formulary drugs may be prescribed by authorized senior doctors for specified less common conditions on a named patient basis).

STEP 4 Educate staff about the formulary list and monitor implementation

All the staff in the hospital must be educated about the list. A common problem is that prescribers continue to request and use medicines not on the list. This results in patients having to buy their medicines from pharmacies outside the hospital, or the procurement group buying non-formulary medicines, without the approval of the DTC. There should be a clear system of implementation, accountability and enforcement including reprimands and sanctions. End users and opinion leaders can be involved in evaluating and enforcing the implementation.

3.2.3 Managing a formulary list (EML): adding and deleting drugs

All applications to add medicines to the list must be made on an official application form (see annex 3.1). Individual doctors making an application must get the endorsement of their head of department. The application should include the following information:

- the pharmacological actions of the medicine and its proposed indication
- why the medicine is superior to those already on the formulary list
- evidence from the literature to support inclusion on the formulary list
- declaration of interest as to whether the applicant has received any financial support from the supplier, i.e. the manufacturing company or wholesaler.

The request should be sent to the DTC secretary who will arrange for the request to be formally evaluated by the responsible person – either him/herself, or a drug information pharmacist, or drug information centre staff.

Evaluations of applications to add new medicines to the list

These should be conducted using explicit documented criteria, preferably evidence-based, as previously agreed by the DTC and covering the following areas:

- **Criteria for consideration of new treatments for conditions not amenable to existing drug therapy, or treatments representing major improvements in survival and quality of life:**
  - — the efficacy, effectiveness and safety of the medicine, as assessed by locally available literature (see section 4.1)
  - — the quality of the drug (which may be considered adequate if registered by the national regulatory body) and a supply chain of acceptable quality (with regard to manufacture, storage and transport)

— whether the hospital has the necessary clinical expertise and laboratory services to use the medicine, and what role specialists should play to regulate therapy

— an estimation of the cost (and potential savings) to the hospital should the drug be introduced – this should include costs of the medicine itself, hospitalization and investigation (see section 4.5)

— availability of the drug on the market.

- **Criteria for treatments representing minor improvements in therapy compared to existing listed medicines. The committee should consider all of the above and in addition:**

  — whether the new drug is really superior to existing ones in terms of efficacy, safety, or convenience of dosing/administration; claimed minor improvements are often proved to be unimportant

  — how the total cost for a course of treatment with the new drug compares with already listed drugs (see section 4.5).

- **Criteria for treatments that are therapeutically equivalent to existing listed medicines. The committee should consider all of the above and in addition:**

  — whether the new drug is really therapeutically equivalent, and not inferior, to existing drugs in terms of efficacy, safety, or convenience of dosing/administration

  — whether the total cost for a course of treatment with new medicine is less than with the already listed medicines (see section 4.5.3).

- **Criteria for use of non-formulary medicines. If the use of non-listed drugs is allowed in certain circumstances, then these drugs need not be included in the list. Such circumstances may include:**

  — non-response or contraindications to available medicines

  — whether to continue therapy for a patient who had been stabilized on a non-listed medicine before admission to hospital and where changing to another drug is considered detrimental.

- **Criteria for restricting the use of certain drugs to specified specialist prescribers only. Such circumstances may include:**

  — the danger of unnecessarily increasing antimicrobial resistance with inappropriate use of third- or fourth-generation antimicrobials; thus they should be limited to prescription by infectious disease or clinical microbiology specialists

  — the danger of serious side-effects that could occur unnecessarily with inappropriate use, for example chemotherapeutic or cytotoxic agents; thus they should be limited to prescription by specialized physicians with knowledge of these medicines.

Written report of the drug evaluation

A written report should be compiled by the person who conducted the evaluation, and discussed at a scheduled DTC meeting. This report should contain the following information:

- the drug monograph, including pharmacology, pharmacokinetics, efficacy as compared to placebo and other medicines, clinical trial analysis (from the literature – see chapter 4), adverse drug reactions, drug interactions, cost comparison
- recommendations based on the evidence-based information

- expert opinions and recommendations from knowledgeable and respected physicians and pharmacists
- how much the new medicine would cost the hospital
- whether the new drug belongs to the national EML and whether it is reimbursable by health insurance schemes.

Discussion and voting procedures

The report should be discussed by the DTC members and a vote taken on the recommendations presented by the person who compiled the drug evaluation report. The final decision should then be disseminated to all health-care staff in the form of minutes, in newsletters and at departmental meetings.

Non-listed requests

A register of all non-listed medicine requests should be kept by the pharmacy and the name of the requesting doctor, the name and quantity of the medicine and the indication for which the medicine was requested should be recorded. When compiled at the end of the year, this information can tell the DTC about prescriber adherence to the formulary list and can also help in deciding whether or not to add drugs onto the list.

Pruning the list

If a new medicine is added to the list for reasons of improved efficacy, safety or lower price, serious consideration should be given to deleting the medicine which was previously on the formulary list for the same indication, for two reasons:

- if the 'new' medicine is better, why continue to have a less good 'old' medicine on the list?
- if no effort is made to consider deleting medicines, none will be deleted and the list will grow in size.

3.2.4 Maintaining a formulary

Routine review of different therapeutic categories is an important part of formulary management. An efficient formulary management process will not passively wait for applications to add new medicines to the formulary. New drugs and treatments are emerging all the time, and without evaluation the formulary may become a collection of older, less effective drugs. Therefore, the entire formulary should be reviewed every 2–3 years. This can be done by evaluating all the formulary medicines within each therapeutic class in a systematic way on a regular basis and comparing them to other new non-formulary medicines within that class. Thus, in order to efficiently maintain a formulary, a DTC should meet regularly to discuss and decide upon:

- requests for the addition of new medicines and deletion of old medicines
- systematic review of a therapeutic class of medicines
- review of programmes to identify and resolve medicine use problems.

All decisions of the DTC should be documented (minuted).

BOX 3.1 PRINCIPLES OF FORMULARY LIST MANAGEMENT

- Select drugs according to the needs of patients
- Select drugs of choice for the conditions identified
- Avoid duplications, both therapeutic and pharmaceutical (dosage forms)
- Use explicit selection criteria, based on proven efficacy, safety, quality and cost
- Use evidence-based information whenever possible
- Be consistent with national EMLs and STGs
- Consider requests for the addition of new drugs only when made by health-care staff, not by the pharmaceutical industry
- Require that requests for the addition of new drugs are justified using documented evidence on efficacy, relative efficacy, safety and comparative cost-effectiveness and that the person requesting any new drug declare any conflict of interest
- Carry out annual systematic reviews of all therapeutic classes to avoid duplication.

3.2.5 Improving adherence to a formulary

The existence of a well-maintained formulary does not mean that prescribers will adhere to it. Methods to promote formulary adherence include the following (see also chapter 7 and MSH 1997, chapter 10 'Managing Drug Selection', chapter 11, 'Treatment Guidelines and Formulary Manuals' and chapter 38 'Hospital Drug Services'):

- reviewing and taking action on all non-formulary medicine use; action may include adding the medicine to the formulary, educating the prescriber about the non-formulary status of the medicines or banning use of the medicine within the hospital
- prohibiting the use of non-formulary drug samples in the hospital
- establishing procedures and approved drug product lists for therapeutic interchange or substitution (see section 7.3.3)
- providing easy access to the formulary list, with copies at each drug ordering location and in pocket manuals for staff
- involving medical staff in all formulary decisions
- advertising and promoting all formulary changes
- establishing agreed procedures for clinical trials with non-formulary medicines.

3.3 Formulary manual

The formulary manual is the publication that brings all the important summary information on medicines in the formulary list together in a manual. There is no set standard on how this document is arranged or what is in the manual. Normally it would contain an alphabetically and therapeutically arranged listing of all the formulary drugs, and a section on drug usage including doses, contraindications, side-effects, drug interactions and price. Ideally the manual should include a section on the medicines of choice and alternates for treating the medical conditions of the region. Annex 3.2 shows a list of the information that should be available in a comprehensive formulary. The DTC may be selective in what information is presented for each item, depending on what has been approved for use locally; for example, including only some but not all dosage forms, strength, indications

for use, etc. A good comprehensive formulary can provide excellent drug information for health-care staff, but developing one is a very time-consuming process. If it is to be used, it will need to be pocket-sized, distributed widely (ideally to every prescriber), regularly updated, and developed in a transparent, participatory way (see section 3.4.2 on STG development). The *WHO model formulary* (WHO 2002b), which is available in electronic format, may be a good starting point for developing a formulary manual.

3.4 Standard treatment guidelines

Even with an ideal formulary list, inappropriate use of formulary drugs may occur. STGs or treatment protocols are a proven, effective strategy to promote appropriate prescribing, when used in conjunction with educational strategies to promote their use (Grimshaw and Russell 1993). STGs may be defined as 'systematically developed statements to help practitioners or prescribers make decisions about appropriate treatments for specific clinical conditions' (MSH 1997). As a minimum, they should contain information on clinical features, diagnostic criteria, non-drug and drug treatments (first-, second-, third-line), and referral criteria (see step 5, section 3.4.2). Contrary to what is often alleged, STGs do not constrain but advise prescribers, who still retain their responsibility to decide upon appropriate treatments. STGs merely define the boundaries between the accepted norms in treating a disease based on good clinical evidence, and the practice of relying purely on clinical experience. The latter provides a very limited scientific basis and is often subject unknowingly to bias and misinterpretation which may result in expensive, inefficient disease management.

STGs are very useful in:

- providing guidance to health professionals on the diagnosis and treatment of specific clinical conditions
- orienting new staff about accepted norms in treatment
- providing prescribers with justification for prescribing decisions made in accordance with STGs
- providing a reference point by which to judge the quality of prescribing
- aiding efficient estimation of drug needs and setting priorities for procuring and stocking drugs.

The problems associated with STGs include:

- a development process which is difficult, time-consuming, and requires human and financial resources
- the need to update regularly to avoid STGs becoming obsolete
- the danger of inaccurate or incomplete guidelines which provide wrong information to prescribers, so doing more harm than good.

Common pitfalls that need to be avoided include, for example,

- including treatment choices that reflect common existing practices rather than best practice according to the evidence
- recommending treatment choices that do not take into account existing expertise or infrastructure.

In Europe there has been a great deal of concern about the quality of STGs and as a result there is now a move to evaluate all STGs according to defined criteria, such as those of the Scottish Intercollegiate Guideline Network (SIGN 1999) or the Appraisal of Guidelines for

Research and Evaluation in Europe, AGREE (Biomed 2000). Since STGs are so important with regard to monitoring and promoting more rational use of medicines, a DTC should be very concerned with developing STGs and promoting their use. Since good-quality STGs are so difficult to develop and implement, the DTC should focus on the most common, clinically important or costliest conditions treated in the hospital. Conditions where treatment is frequently suboptimal or wasteful may also be the focus of STG development.

3.4.1 Developing, adapting or adopting standard treatment guidelines

STGs can range from protocols covering diseases commonly seen in primary health care to those seen only in major medical centres and tertiary hospitals. An STG manual may contain a few or many clinical conditions. The DTC can develop new STGs from scratch – a very difficult and time-consuming activity, which may be appropriate for large hospitals. Alternatively, the DTC may adapt existing national or institutional STGs to form their own local version, or simply advocate the use of existing STGs published by other groups.

Adaptation or adoption of existing STGs is much easier and may be especially appropriate for small hospitals with inexperienced DTCs. Some guidelines are freely available on the web such as those from South Africa (Essential Drugs Programme South Africa 1998) and Australia (Therapeutic Guidelines Ltd 2000). Development and publication of a hospital's own STGs, with its own book cover, may create a sense of ownership and acceptance of the guidelines. However, the DTC will need to decide whether this sense of ownership will promote the use of the STGs sufficiently to justify the extra work involved.

Whatever option is chosen, the DTC should:

- document and disseminate its choice, and the rationale for that choice, to all health workers
- ensure that any STGs developed, adapted or adopted are consistent with national STGs and the guidelines of any national disease programmes (sexually transmitted infections, HIV/AIDS, malaria, diarrhoeal disease, tuberculosis (TB) and acute respiratory infections)
- ensure that all prescribers have a copy of the chosen STG; this may mean paying for the publication of an STG manual and giving one copy to each prescriber for personal use rather than relying on prescribers buying a copy
- make provision for review and updating of any guidelines that are developed
- educate all prescribers in the use of STGs
- do follow-up and give feedback on whether prescribers are adhering to the STGs (see sections 6.3, 6.5 and 7.3.2).

3.4.2 Steps in developing and implementing STGs

Credibility, ownership, and hence use, will be increased if the development process uses evidence-based medicine, is participatory, is documented, and all contributors are acknowledged. It is important to document the affiliations of the contributors so that prescribers can see that authors had no conflict of interest, for example business interests with a local manufacturer or wholesaler. The procedure may follow the steps listed below.

■ STEP 1 Identify the working group to adapt/develop the hospital STGs

The DTC may give responsibility for drafting the guideline, searching the literature and reporting back to the DTC on progress, to one or two DTC members or to a working group or subcommittee. Whoever is chosen, it is important that staff from all departments, including general practice, clinical pharmacy and pharmacology, be encouraged to comment

on the draft. They should be provided access to the information upon which the DTC will base its decisions. Hospitals without sufficient clinical experts should get an external consultant group to assist in developing, adapting and updating the STGs.

STEP 2 Develop an overall plan for developing and implementing the STGs

It is not enough merely to identify a working group and experts. The DTC should agree and document who will be responsible for drafting the STGs, who will review them and who will edit them. Other things that need to be agreed include a format, a budget, and what kind of information will be used. It is useless to put a vast amount of effort into developing STGs that will not be used by prescribers or supported by hospital management (in terms of distribution or inclusion in pre- or in-service training), so a plan and budget should also be made at this stage for publication, dissemination and implementation (see step 7).

STEP 3 Identify the diseases for which STGs are needed

Each department should be asked to identify the most common diseases in their specialty area, for both outpatients and inpatients. The list of diseases as identified by the different departments should be consolidated and ranked based on prevalence, severity, impact on general health of the population and the cost to the hospital of treating the condition. Some diseases, such as skin diseases, contribute substantially to the number of patients treated and the cost of drugs provided, but cause little significant morbidity or mortality. In some situations the DTC may decide not to select all the common diseases or problems but select a small number of problems or diseases:

- where there is variation in practice and inappropriate use is known to occur
- which are not covered in other published STGs
- which are expensive to treat or which are treated with drugs that are dangerous to use, for example cancers treated with cytotoxic drugs or diabetes treated with insulin.

STEP 4 Determine the appropriate treatment

This step is critical to the development of any new STGs. Experts and clinical specialists should consider the evidence concerning appropriate treatment for each disease or clinical problem and reach a consensus based as far as possible on evidence-based information sources. Consistency with national STGs is important and recommended treatments should:

- consider non-drug treatments
- use the fewest medicines necessary
- choose the most cost-effective treatments
- use approved formulary list drugs only (although the formulary list may need to be changed according to a review of the evidence)
- identify first-, second- and if necessary third-line drugs
- determine dose and duration, contraindications and side-effects for all medicines recommended
- take into account
  - — the existing level of prescribers (and their diagnostic skills)
  - — the hospital facilities and monitoring capacity
  - — the affordability and availability of the drug of choice in the market.

STEP 5 Determine what information should be included in the STGs

The decision on how much information to include must be weighed carefully. A small book that fits into the prescriber's pocket will be used more readily than a large comprehensive textbook that is kept in the library. It is always important to state clinical signs and symptoms, diagnostic criteria, drugs and dosage, clearly and concisely, but other information may be omitted. Instead, the users may be referred to more comprehensive guidelines and references that should be made available in the hospital library or drug information unit/centre. Information that may be included in hospital STGs includes the following:

- clinical condition, its natural history and diagnostic criteria, including signs and symptoms and laboratory tests
- treatment objective, for example elimination of *Plasmodium* parasites from a blood smear, sputum negativity in a previously sputum-positive TB patient
- non-drug treatment
- the drug of choice for the specific disease/condition
- alternative second- and third-line drugs, together with their indications
- relevant prescribing information – dose, duration, contraindications, side-effects, warnings, toxicity and drug interactions
- referral criteria
- what to tell the patient
- cost of treatments, especially if alternatives are proposed.

STEP 6 Draft the STGs for comments and pilot test

STGs generate widely varying opinions especially among prescribers, who are unlikely to use them unless they have been involved in the development process and a consensus is reached during drafting. Thus, the draft should be circulated widely and relevant comments incorporated. In order to ensure that comments are constructive, it may be helpful to ask for responses to be given in a structured way. For example, one may ask:

- what should be changed and how
- why it should be changed, providing evidence and justification.

Once the content of an STG is agreed, a draft should be pilot tested in order to ensure that the document is clear and easily understood and the information is accurate. The size, presentation of information and layout can affect how easy a document is to read and use. Piloting STGs may be done by circulating the draft to a number of prescribers and finding out if they are able to use the draft STG.

STEP 7 Implement – publish, launch, disseminate, train and supervise

Once the final draft is approved by the DTC, it can be published and distributed to staff. Distribution should be accompanied by an official launch, some initial training for staff on the STG, its importance and how to use it. Thereafter, follow-up (in-service) training, monitoring of adherence to STGs and supervision should be carried out (see chapters 6 and 7). As with formulary manuals, use will be enhanced if the STGs come in a pocket-size format and are distributed as widely as possible, ideally to every prescriber. Use of the STGs will also be encouraged if there is consistency of medicine selection between the STGs and the formulary list.

STEP 8 Update

Treatments can change rapidly, for example with the emergence of new drugs or new patterns of antimicrobial resistance. Thus, STGs must be updated regularly by reviewing the local antimicrobial susceptibility pattern, and other sources of information from evidence-based sources (for example reputable textbooks, drug and therapeutics bulletins or respected medical journals). The various experts and clinicians within the hospital should keep abreast of the current developments in drugs and therapeutics within their own disciplines, and inform the DTC appropriately. Once the DTC has received and accepted a sufficient number of requests for treatment revisions, the STGs can be updated. Between editions of the STGs, new information can be disseminated through circulars or drug bulletins. Unless the STGs are updated regularly (every 2–3 years) using data sources that all staff agree are acceptable, the STGs will quickly lose their credibility.

ANNEX 3.1

Application forms to be filled in by applicants when applying for a new drug to be added to the hospital formulary list

In a Zimbabwean hospital

Applicant's name:	Signature:	Date:
Generic name:	Therapeutic class:	
Trade name and supplier:		
Unit cost:		
Is this drug on the national formulary list?		
Proposed indications for use:		
Principal mode(s) of action:		
Major adverse effects and drug interactions:		
Precautions and contraindications:		
State prescribing restrictions, for example 'specialist only':		
Are there prescribing guidelines?	Please attach	
Average dose and frequency:		
Average duration of therapy:		
List drugs already approved for same indication:		
List drug(s) to be replaced by requested drug:		
Estimated number of patients per year:		
Estimated annual expenditure on drug:		
Advantages over listed alternative(s).	Please attach references.	

Source: Zimbabwe DTC manual (1999).

In a Nepali hospital

Patan Hospital Formulary Committee

Application for Inclusion of drug in Formulary

Date:

Application reference.

[Please be brief and try to include all relevant information below. PLEASE DO NOT WRITE IN THE SPACE BELOW THIS LINE. If necessary, a continuation sheet may be attached.]

Drug name (generic)

Drug name (trade)

Dosage form and strength

Therapeutic category

Why is this drug being proposed?

Does another drug of this category already feature in the Formulary? Yes / No

If "yes": (1) list the advantages of the proposed drug over the present Formulary entry.

(2) should the existing formulary entry be replaced by the proposed drug? Yes / No

Please list any contra-indications, precautions and toxic effects of the proposed drug

Please add any additional information (e.g. references to published papers) in support of this application

Submitted by of Department

Head of Department.

Committee Decision:

Registered with D.O.A. for use in Nepal?

Date: Signed

In a South African hospital

4 APPLICATION TO THE KWAZULU-NATAL PHARMACY AND THERAPEUTICS COMMITTEE

ALL QUESTIONS MUST BE ANSWERED FULLY

1.1 Pharmaceutical product

Approved name

Trade Name

Manufacturer

Presentation (tablets, syr

Strengths

1.2 List the specific clinical indication for the product in KwazuluNatal

1

2

1.3 Indicate the suggested level of prescribing (Please tick)

Medical Officer Community Health Worker Registrar

PHC Nurse Consultant Specified Clinic

2.1 List the institutions or Units in KwazuluNatal that will require the product

2.2 Estimate the annual number of patients for this product in the KZN.

2.3 State the clinical justification for the listing of this drug

In a South African hospital *(continued)*

2.4 Request

(please tick) Which agent ?

[redacted]

2.5 Compare the requested drug to other available drugs (include all from within the same pharmacological group.

2.6 Full motivation and supporting literature (include package insert and approx 3 key references). Please discuss each drug mentioned above with regard to efficacy, side effect profile, compliance and cost effectiveness (which includes value for money, prevention of hospitalisation, duration and effect on attendance).

3.1 If approved, would a cost saving would be effected? If so, please indicate where. (Please tick)

In a South African hospital *(continued)*

Duration of hospital stay

Laboratory tests

Other diagnostic tests

Outpatient attendances

Nursing services

3.2 Will the current Standard Treatment Guidelines (Green, Yellow or Purple Book) need to be amended?

YES/NO

If yes, are there any appropriate guidelines to support the rational use of the drug? If so, please provide these as an annexure to this form. If not, please draft suitable guidelines.

3.3 Have you ever used samples of the drug requested ? YES NO

Have you ever used the drug in a clinical trail or assessment ?

YES NO

Have you attended a conference with sponsorship from the manufacturers of the drug within the last two years ?

YES NO

Have you or your department received funding, grants, or any equipment or supplies from the manufacturers of the drug within the last two years ?

YES NO

If any of your answers to the above questions are "Yes", please provide the full details as an annexure to this form

4.1 Motivation prepared by:

Name	Designation / Department	Signature

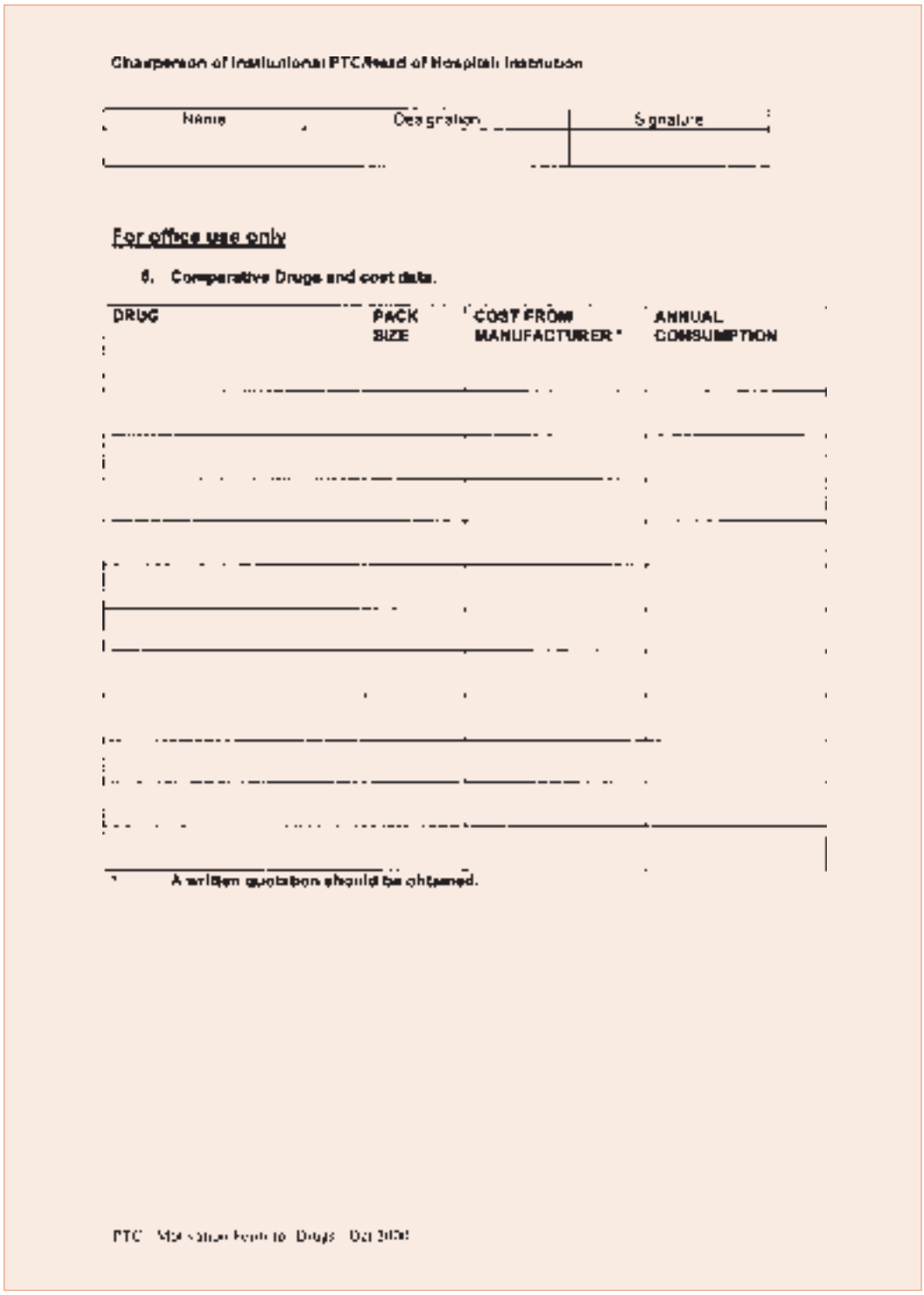
Hospital/Institution:

4.2 This request has been discussed by the District/Hospital Pharmacy and Therapeutics Committee and is:

supported/ not supported.

PTC - Motivation form for Drugs - Oct 2004

In a South African hospital *(continued)*



Chairperson of Institutional PTC/Head of Hospital Institution

Name | Designation | Signature

For office use only

6. Comparative Drugs and cost data.

DRUG	PACK SIZE	COST FROM MANUFACTURER *	ANNUAL CONSUMPTION

* A written quotation should be obtained.

PTC Manual: Guide to Drugs Oct 2004

ANNEX 3.2

Drug information included in a comprehensive formulary

1	Formulary list or essential medicines list	Alphabetical and therapeutic category lists
2	Brief information about each medicine	Generic name Dosage and strengths Indications, contraindications and precautions Side-effects Dosage schedule Instructions and warnings Drug, food, laboratory interactions
3	Supplementary information for medicines	Price Regulatory category Storage guidelines Patient counselling information Labelling information Brand names and synonyms
4	Prescribing and dispensing guidelines	Rational prescribing techniques Principles of prescription writing Guidelines for quantities to be dispensed Controlled drug requirements Adverse drug reaction reporting requirements Dispensing guidelines List of precautionary labels Common drug interaction tables
5	Treatment protocols	IV drug administration guidelines Drugs used in pregnancy and lactation Drugs used in renal failure Poisoning (intoxication) guidelines Prescribing in the elderly
6	Other components	Metric tables Adverse drug reaction form Formulary request form Indexes Abbreviations

4. Assessing new medicines

Summary

The assessment of new medicines is critical to managing a formulary list, which involves adding new medicines and deleting old ones. Drugs should be evaluated and compared on the basis of:

- efficacy, comparative efficacy
- effectiveness, comparative effectiveness
- safety, comparative safety
- cost of use
- quality.

Efficacy, effectiveness and safety can be evaluated from a critical assessment of the literature. Much of the information may be biased and it is very important that those evaluating new medicines have the necessary skills and time to assess the literature critically. Once efficacy and safety are established, medicines should be compared according to cost of use and, if possible, cost-effectiveness. Drug costs and quality will vary with locality.

4.1 The need for critical assessment of new medicines

There has been an incredible increase in the number of drugs marketed over the past 20 years and today there are over 100 000 pharmaceutical preparations on the world market. Pharmaceutical manufacturers not only research and develop drugs for the ultimate goal of treating and preventing disease, but also for high profits. In order to make available a reasonable number of medicines that are effective, safe, of desirable quality and of reasonable cost, the DTC must take meaningful steps to review medicines and select the most appropriate ones available.

New medicines should be evaluated on the basis of efficacy, safety, quality and cost. Assessment of efficacy can only be done by critical assessment of the drug literature. Assessment of safety must also be done through critical review of the literature as well as monitoring adverse drug reactions (section 5.4). Quality (section 5.3) and cost (section 4.5) will vary with local circumstances, but even here international publications may play a role in providing information about specific relevant issues. For example, bioavailability of combination TB drugs is known to be problematic and many manufacturers in developing countries do not have the capacity to test for adequate bioavailability. The *International price indicator guide*, published by Management Sciences for Health (website http://www.msh.org), provides international cost comparisons for most drugs on the WHO model essential medicines list (EML) (WHO 2002a); this helps to decide whether certain drugs merit the price. Finally, assessment of whether the benefits of a medicine are worth the cost, i.e. cost-effectiveness, can often only be done by critical review of pharmacoeconomic evidence. Since much of the literature is difficult to interpret and often biased, cost-

effectiveness and benefit analyses can usually only be done by experts at the national level.

4.2 Sources of information to assess new medicines

Adequate resources to obtain information and to evaluate drugs are essential. Medical information sources include three categories: primary, secondary, and tertiary. Addresses and websites are provided in annex 4.1.

- The **primary literature** includes journal articles and unpublished studies. These may be obtained from journals and services (electronic or otherwise) that provide the entire articles. An original article contains the most complete information about a subject because readers have access to all the data and study methods and therefore can draw their own conclusions. The disadvantages are that readers must have sufficient time to read and evaluate the article, the skills to evaluate it and compare its information with that in other articles.
- The **secondary literature** includes indexing and abstracting services that provide abbreviated reviews of articles. Such literature is usually published in newsletters, CD-ROM databases and online services, for example the Cochrane Library. The main advantage of such information sources is that the information is accessible and easy to read. A disadvantage may be the length of time between publication of the original data and its republication in a newsletter or abstracting service.
- The **tertiary literature** consists of published textbooks. These are usually very good sources of information if reputable and current sources are used. The advantage of textbooks is that one can read and assimilate the information in a relatively short time, since all the information is in one volume. The disadvantages are the lack of access to the original information sources, bias introduced by the writers of the text, and information becoming outdated because of long delays in publishing a text.
- **Information from pharmaceutical companies** should be used with caution, since such information is biased in favour of positive results in order to promote sales. These materials are usually tailored to the various health professions. They may take the form of scientific articles in professional journals, symposia proceedings, news reports or pamphlets distributed by drug representatives. See also section 7.4.2
- The **Internet** is a rapidly expanding source of drug information. Although pharmacists or physicians in many parts of the world may not have Internet access, it is a resource that should be used if at all possible. However, it is best to use only those sources that have been recommended by reputable sources and to verify the source of information available on the Internet (WHO 1999b), as the quality of drug information from other sources may be either good or poor.

4.3 Assessing the efficacy and safety of new medicines from the literature

Ideally, the hospital will have a drug information centre to handle requests concerning adding drugs to the formulary or requesting changes to the STG. If not, a pharmacist or a physician can provide the necessary drug evaluations, given the time and at least some of the resources listed above. However, very few pharmacists or physicians take the time or have the skills to accurately evaluate a journal article describing a drug study. Health professionals frequently read the abstract and conclusions with little or no attention to the structure and validity of the written article. They may therefore fail to recognize articles based on poorly designed studies with inaccurate or invalid conclusions. National DTCs and tertiary hospitals must review the primary literature, i.e. the actual drug studies.

However, for most hospital or sub-national DTCs, review of good-quality secondary or tertiary literature should be sufficient. It is not necessary for different centres to all review the same literature, nor do most of them have the time and capacity to do so.

Discussion of critical review of the primary literature is beyond the scope of this manual. However, it is important that DTC members have some skills in this type of critical review in order to better assess and use commonly available secondary and tertiary literary sources and literature from the pharmaceutical industry. For literature concerning a new medicine to be sufficient for a DTC to decide whether to add or delete a medicine from the formulary, it should:

- **Compare the drug of interest to another standard drug in its class** and not just to a placebo or another drug of poor performance. Unfortunately in many studies a new drug is compared only to a placebo or to a drug of poor performance.
- **Test the drug of interest in patients that are representative** of those who would take the drug in the DTC's institution and not just in healthier 'study patients'. Whether the sample of patients is representative and relevant can only be judged by a description of the inclusion and exclusion criteria for patients in the study.
- **Measure clinically important outcomes**, for example blood pressure or blood sugar, using established methods, for example relative or absolute risk reduction (see section 4.4); the amount by which a clinical outcome is improved (for example mmHg for blood pressure) is just as important as whether the difference between one medicine and another is statistically significant.
- **Use adequate study design**, preferably a randomized controlled trial (see section 7.6), and test the medicines in a sufficient number of patients; this is necessary in order to ensure that any observed effects are not due to factors (confounders) other than the medicine being tested and are also not due to chance. Trials comparing a drug against a placebo will require at least 40 patients to demonstrate symptom relief and usually several thousand patients to demonstrate a reduction in mortality. Several hundred to several thousand patients are required to show superiority of one drug over another.
- **Take adequate precautions to ensure that the results are not biased**. If possible, patients, prescribers and any researchers judging clinical outcomes, should be blinded to which medicine a patient is taking; this will ensure that their opinions do not influence the results (measurement bias). Patients should be randomly selected to receive the new drug, comparator drug or placebo and the random selection process concealed from patients and professionals alike; this will ensure that there are no differences that could influence the results between patients receiving the new drug and those receiving the comparative drug or placebo (selection bias).
- **Apply appropriate statistical analysis to the results.**
  - **p values** of less than 0.05 are taken by convention to mean that the results of a study are not due to chance. A p value of 0.05 indicates that there is a 1 in 20 probability that any study result is due to chance, meaning that there is a 5% chance of observing a result which does not exist in the population. This means that there is a 95% chance that any difference observed, for example, between the drug of interest and the comparator drug, is a true difference in the population.
  - The **power of a study** indicates the likelihood of a hypothesized result being observed and is dependent on sample size. A value of 80% is taken by convention to be the minimum and indicates that there is an 80% chance of observing a real difference, for example, between the drug of interest and the comparator drug, meaning that there is a 20% chance of not observing a difference that really exists in the population.

— The **confidence interval** indicates the range within which the true study results lie. By convention 95% confidence intervals are used and indicate that there is a 95% chance that the true result lies within the estimated or observed range. The larger the sample size the narrower the confidence interval of an observed value (for example, mean reduction in blood pressure or percentage of patients with pain relief).

- **State its funding sources and whether it has been peer reviewed**; this is necessary because studies funded by the pharmaceutical industry are often only published if they are positive and in journals that are peer reviewed less strictly or not at all.

More detail about common problems seen in many drug studies is summarized in annex 4.2, with a checklist to use when critically reviewing articles.

4.4 Measuring and comparing clinical treatment outcomes

In order to interpret the results of studies, the treatment outcomes need to be presented in a way such that the relative benefits of one medicine over another or over placebo can be easily seen. A number of particular measures are described below, and a practical example of using such measures is given in box 4.1.

- The **event rate** is the rate of a particular event (for example treatment outcome) in both treatment and control groups.

  event rate = events in group/number of subjects in group

- The **relative risk** (RR) is the ratio of the incidence of an event occurring in the treatment group to the incidence of an event occurring in the control group. If the RR < 1, then the event is less likely to happen in the treatment group than the control group and if the RR > 1, then the event is more likely to happen in the treatment group.

  RR = event rate in treatment group/event rate in control group

- The **relative risk reduction** (RRR) is the difference between the event rates in the treatment (experimental) and control groups as a proportion of the event rate in the control group. This is a measure of relative treatment efficacy within the study population.

  RRR = (event rate in control group – event rate in treatment group)/event rate in control group

- The **absolute risk reduction** (ARR) is the difference between the event rates in the treatment (experimental) and control groups. This is an absolute measure of efficacy and may often be much lower than the relative efficacy (see box 4.1).

  ARR = event rate in control group – event rate in treatment group

- The **number needed to treat** (NNT) is the number of patients who need to be treated to achieve one additional favourable outcome. It is the reciprocal of the ARR (the number 1 divided by the ARR). This calculation provides the reader with an easier interpretation of the results, one that can be compared to other treatment groups and treatment modalities.

  NNT = 1/ARR

4.5 Measuring and comparing drug costs

Evaluating a new medicine for the formulary involves not only efficacy, safety and quality, but also cost and cost-effectiveness. A simple determination of price is inadequate for determining the actual cost of a medicine for the health-care system. This section provides

BOX 4.1 THE HELSINKI HEART STUDY

4081 asymptomatic men, aged 40–55 years, with dyslipaemia (total cholesterol minus HDL >5.2 mmole/l), were enrolled in a 5-year double-blind randomized study to compare gemfibrozil 600 mg twice daily with matched placebo. The number of events (fatal and non-fatal myocardial infarction and other cardiac death) was measured.

	Gemfibrozil	Control
Number of events	56	84
Number of subjects	2051	2030
Event rates	56/2051 = 2.73%	84/2030 = 4.13%

relative risk (RR) = 2.73/4.13 = 0.66
i.e. gemfibrozil was associated with less risk of an adverse event

relative risk reduction (RRR) = (4.13 – 2.73)/4.13 = 33.9%
i.e. there was a large relative reduction (33.9%) in risk

absolute risk reduction (ARR) = 4.13 – 2.73 = 1.41%
i.e. only a small number of cases will benefit from the decreased risk

number needed to treat for 5 years to prevent one event (NNT) = (1/1.41%) = 100/1.41 = 70.9
i.e. 71 patients need to be treated with gemfibrozil for 5 years to see an effect in one patient

The researchers concluded that although gemfibrozil was associated with a relatively large reduction in risk (33.9%) of adverse event, the actual numbers of patients normally suffering such events is in fact very small, so the resulting reduction in absolute risk is small (1.41%). Thus, a large number of patients (70.9) must be treated over 5 years in order for one patient to avoid an adverse event. In addition, 2.4% of cases taking gemfibrozil suffered from moderate to severe upper gastrointestinal symptoms, as opposed to 1.2% of cases taking placebo. Taking side-effects and cost into account, many countries and hospitals may decide that the efficacy is not sufficient to justify the cost and increased risk of side-effects.

(Frick et al. 1987)

basic summary information on how to evaluate the cost of a drug, and compare different drugs, not only in terms of procurement costs, but also in terms of cost impact on the health-care system and patient outcome. Detailed description of pharmacoeconomic methods is beyond the scope of this manual and unnecessary for the average hospital DTC member to know. Nevertheless, it is important for DTC members to understand the basic principles of various pharmacoeconomic methods in order to better understand the literature on drug cost-effectiveness and cost benefit.

4.5.1 Price of a drug

The unit acquisition price (for example the cost of a tablet or vial) from a supplier is the easiest and most obvious measure of drug cost that is available to the DTC. Comparison of prices is useful when comparing drugs which are exactly the same chemical entity and dosage form but produced by different manufacturers. Price and other supplier considerations (such as reliability and quality) are compared when choosing which drug product to procure. Usually it is the procurement department that will make such comparisons, but the DTC may have a role to play in deciding whether the different brands are bioequivalent. When comparing medicines of a different chemical entity, even if they have equal therapeutic effect, unit price alone is inadequate for comparison. This is because the unit dosage or

treatment duration or mode of administration to achieve the same clinical result will not be the same for the different medicines.

4.5.2 Cost of a drug

The acquisition price from a supplier may be the most basic cost of a drug, but is not the complete cost of using the drug. When choosing between different medicines of the same therapeutic class for inclusion in the formulary, the DTC will want to know the cost of using the medicine, not merely the price of an individual tablet or vial. There are three types of cost associated with drug use in a health-care system: direct, indirect and intangible.

- **direct costs**
  - — acquisition cost of the drug or drug price
  - — supplies to administer the medicine
    equipment for administration, syringes, gauze, IV sets, filters, pumps, etc.
  - — supply management costs
    salaries of supply staff, transport costs and storage facilities (including warehouse, refrigerator, freezer)
  - — professional services costs
    pharmacist salary, preparation and dispensing of medications
    clinical pharmacy activities
    nursing salaries, physician fees
  - — other direct costs
    treating adverse drug reactions
    inpatient and outpatient treatment of poor response to drug therapy
    emergency room use
    hospital overhead costs, for example electricity
    laboratory services
- **indirect costs**
  - — cost of illness to the patient
  - — lost time from work
- **intangible costs**
  - — quality of life.

Although these three costs, taken together, give the most comprehensive assessment of actual drug cost, they will usually only be analysed at national level or for comparative cost-effectiveness studies. Such a comprehensive cost analysis is necessary when deciding what medicines should be on a national EML, but there is no need for every hospital DTC to re-do all such analyses. However, the DTC may wish to evaluate all the direct costs of using a new drug in order to assess whether there is sufficient budget to add it to the formulary list.

4.5.3 Cost minimization analysis

Cost minimization (cost identification) analysis is a method of comparing two or more medicines of equal therapeutic effectiveness and safety to find out which one is the cheapest. This method of cost evaluation is the one used most often by pharmacy departments; it can be used to compare

- different brands of the same drug, or

- therapeutically equivalent drugs, which are not the same chemical entity but belong to the same therapeutic category and can be used interchangeably.

Such comparison can be difficult for many medicines, as there may not be a reliable measure of equivalence between the two products. If therapeutic equivalence cannot be demonstrated then this particular type of cost comparison should not be used. When therapeutic equivalence between a new and an old drug is studied, the sponsor of the new drug should provide proof of superiority and non-inferiority. Cost minimization should also reflect the cost to prepare and administer a dose:

- pharmacist and nursing time for preparation
- laboratory costs
- cost of any ancillary equipment, for example syringes, needles, IV sets, sterile diluents.

Table 4.1 shows a cost minimization analysis of three oral antimicrobial drugs to treat uncomplicated urinary tract infection. The analysis shows that trimethoprim was the cheapest medicine. Although norfloxacin was more expensive than amoxycillin with regard to loose tablets/capsules this was not so with regard to prepackaged courses of treatment. The assumption that there is therapeutic equivalence may not be true in areas with high rates of antimicrobial resistance. Furthermore, the different rates and cost of side-effects have not been taken into account.

Table 4.1 **A cost minimization analysis of three antimicrobial drugs to treat uncomplicated urinary tract infection**

Cost categories	Trimethoprim 200 mg tab.	Amoxycillin 500 mg cap.	Norfloxacin 400 mg tab.
Recommended treatment regimen for uncomplicated urinary tract infection	200 mg twice daily x 5 days	3 g twice daily x 1 day	400 mg twice daily x 3 days
No. tabs/caps per course of treatment	10	12	6
Acquisition price for 1 loose tab./cap.	£0.048	£0.088	£0.365
Price for course of treatment	£0.48	£1.06[a]	£2.19[b]
Cost to treat 10,000 patients per year	£4,800	£10,600	£21,900

Treatment regiments and prices were taken from the *British National Formulary* 2002.
[a] Amoxycillin sachets: price for prepackaged course of treatment was £4.16.
[b] Norfloxacin tablets: price for prepackaged course of treatment was £2.19.
£1 = US$ 1.5 approximately.

Table 4.2 shows a cost minimization analysis of three injectable narcotic analgesics, one of which (diamorphine) is given by two routes. The analysis shows that pethidine intramuscular (IM) or subcutaneous (SC) injection is the cheapest option. Diamorphine given by slow intravenous (IV) injection is the most expensive option.

Table 4.2 **Hypothetical example of a cost minimization analysis of three injectable narcotic analgesics**

Cost categories	Diamorphine 5 mg vial		Pethidine 50 mg vial	Pentazocine 30 mg vial
Recommended treatment regimen for severe pain requiring injectable analgesia	5 mg 4 hourly IV	5 mg 4 hourly IM or SC	50 mg 4 hourly IM or SC	30 mg 4 hourly IM or SC
Acquisition price for one vial (US$)	1.84	1.84	0.83	2.61
No. doses needed per day	6 doses/day	6 doses/day	6 doses/day	6 doses/day
Price for one day's treatment (US$)	11.04	11.04	4.98	15.66
Nursing salary @ US$2.00 per IM or SC injection	–	12.00	12.00	12.00
Specialist nursing salary @ US$4.00 per slow IV injection	24.00	–	–	–
Equipment: syringe + needle US$2.00 per set	12.00	12.00	12.00	12.00
Total drug costs per day (US$)	47.04	35.04	28.98	39.66
Anticipated no. days treatment per year	3000 days	3000 days	3000 days	3000 days
Total drug costs for 3000 days treatment (US$)	141,120	105,120	86,940	118,980

Treatment regimens and prices were taken from the *British National Formulary* 2002 and converted into US$; equipment prices were from the Drug Tariff November 2002, UK Department of Health, and salary estimated for 3 minutes per IM or SC injection and 6 minutes per slow IV injection.

Sensitivity analyses are very important in any kind of economic analysis. Such an analysis tests how sensitive the conclusions are to the different assumptions made. For example, in table 4.2, if we change the assumption that IV injections take twice as much nursing time as SC or IM injections, and assume instead that IV, IM and SC injections take equal nursing time, then IV diamorphine would cost less than IM or SC pentazocine.

4.5.4 Cost-effectiveness analysis

Cost-effectiveness analysis is used to compare two or more medicines which are not exactly equivalent in terms of dose or therapeutic effect, but which are used to treat the same clinical condition. This form of analysis is difficult and is often only done at the national level. It requires measuring the cost per defined measurable clinical outcome (effect) for each of the drugs. The cost of the drug should include indirect as well as direct costs and some examples of measures for clinical outcomes include:

- hypertension – blood pressure measurements
- diabetes – glycosylated hemoglobin, blood glucose results
- coronary heart disease –frequency of angina attacks
- urinary tract infections – incidence of infections
- obesity – weight measurement
- seizures disorders – frequency of seizures
- HIV/AIDS – CD4 counts
- heart failure (and any other disease) – years of life saved or quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs).

Cost-effectiveness measurement can be presented in many different ways. Some examples include:

- for acute illness: cost per course of treatment or cost per cure
- for chronic illness: cost per month of satisfactory control
- for disease prevention: cost per case prevented
- for health promotion: cost per month of desired outcome.

Table 4.3 shows an example of a cost-effectiveness analysis to compare two types of antibiotic ear drop. Ear drop A costs US$6.50 and has been found to be 80% effective; ear drop B costs US$7.90 and has been found to be 90% effective.

Table 4.3 **Hypothetical example of a cost-effectiveness analysis for two antibiotic ear drops**

	Ear drop A	Ear drop B
Cost (US$)	6.50	7.90
Effectiveness	80%	90%
Cost-effectiveness	US$6.50 to treat 0.8 of one case successfully	US$7.90 to treat 0.9 of one case successfully
Amount (US$) needed to treat one case successfully	6.50/0.8 = 8.125	7.90/0.9 = 8.778

Thus, although ear drop A was less effective than ear drop B, it was found to be more cost-effective in terms of the amount needed to treat one case successfully. The additional cost of B was not worth the small extra benefit. The additional cost for extra benefit, known as **incremental cost-effectiveness**, can be calculated as follows for this example:

(7.90 – 6.50)/(0.9 – 0.8) = 1.4/0.1 = US$14.00

Is it reasonable to pay an extra US$14 per additional case successfully treated? This judgement will need to be made by the DTC.

Steps for conducting a cost-effectiveness analysis

1 Define the objective of the analysis, for example which drug regimen should be the treatment of choice?

2 Identify the different ways to achieve the objective, for example should we use a cheaper slightly less efficacious medicine or a more expensive and slightly more efficacious one?

3 Identify and measure the drug costs of each option.

4 Identify and measure the benefits (clinical outcomes) of each option.

5 Calculate and interpret the benefits of each option. The cost-effectiveness ratio is the total drug cost divided by the number of units of outcome.

6 Perform sensitivity analysis on the conclusions. This is where some of the assumptions in the analysis, for example costs of staff salaries and hospital overheads, are varied to see if changing these assumptions also changes which medicine is found to be most cost-effective. If the conclusion about which medicine is most cost-effective does not change with varying the assumptions, then the conclusion is likely to be valid. If however, the conclusion is very sensitive to changing the assumptions, then the study result is likely to be subject to error and no firm conclusion can be drawn.

Box 4.2 shows a real example of how two different kinds of thrombolytic agent for the treatment of myocardial infarction were compared from the point of view of efficacy and cost-effectiveness in Australia. The treatment of myocardial infarction in the usual way was compared with usual treatment plus the use of either streptokinase or plasminogen activator. Comparison was done in terms of (1) total treatment costs, (2) death rates, and (3) cost per life saved (or death averted). The treatment costs included all the direct and indirect costs mentioned in section 4.5.2.

4.5.5 Cost utility analysis

Cost utility analysis is a cost-effectiveness analysis, where a composite measure of effectiveness is used to reflect both the quantity and the quality of health outcome. Examples of utility measures are **quality adjusted life years** (QALYs) or **disability life years** (DALYs). As well as measuring outcome of cases cured, deaths averted, or lives saved, these measures take account of the fact that impairment, discomfort and handicap mean that a 'life-year' is sometimes too crude a measure of effectiveness to capture all that is clinically important. A quality adjustment factor is normally obtained through surveys where people are asked to indicate their preferences between different states of health. Because of the difficulty of assessing quality of life, this method is controversial for comparing medicines and is likely to be beyond the scope of a DTC.

4.5.6 Cost benefit analysis

In cost benefit analysis, there is calculation of (1) the cost of the medicine, and (2) the monetary value of the benefits or change in outcome. Such benefits should measure the total gain in economic welfare associated with the intervention. This is sometimes broken down into the value of healthy time gained, savings in treatment costs, and other savings or benefits. The selection and valuation of benefits is often controversial and incomplete. Cost benefit analysis is very controversial because of placing a monetary value on clinical outcomes such as life years saved.

The **cost benefit ratio** is the total drug cost divided by the monetary benefit (in terms of money saved by using the drug, for example less future illness, less hospitalization, etc.). Unlike cost-effectiveness analysis, where comparable medicines are analysed for the same outcome, cost benefit analysis can be used to compare different treatments with different outcomes. However, cost benefit analysis is very difficult to do, requires major assumptions that may be incorrect, and is unlikely to be useful for most DTCs.

BOX 4.2 ECONOMIC ANALYSIS OF TWO THROMBOLYTICS IN ACUTE MYOCARDIAL INFARCTION

A review of the literature concerning the cost-effectiveness of different thrombolytics in the treatment of myocardial infarction was conducted in Australia. The cost of the various treatments and the mortality rate following myocardial infarction were evaluated and the results are shown below. Prices are given in Australian dollars (AUD).

Cost of treatment and mortality rates

Usual care of myocardial infarction (MI):	AUD 3.5 million/1000 cases, 120 die
Usual care of MI + streptokinase (SK):	AUD 3.7 million/1000 cases, 90 die
Usual care of MI + plasminogen activator (TPA):	AUD 5.5 million/1000 cases, 80 die

Comparison of the different treatments

Difference between SK and usual care of MI:

Cost of treatment = AUD3.7–3.5 million/1000 cases = $0.2 million/1000 cases = AUD200/case
No. of deaths that will be prevented = 120–90 = 30 deaths/1000 cases treated
Cost-effectiveness of SK = AUD0.2 million/30 lives = $6700 per life saved

Difference between TPA and usual care of MI:

Cost of treatment = AUD5.5–3.5 million/1000 cases = 2.0 million/1000 cases = AUD2000/case
No. of deaths that will be prevented = 120–80 = 40 deaths/1000 cases treated
Cost-effectiveness of TPA = AUD2.0 million/40 lives = $50 000 per life saved

Difference between TPA and SK treatments for MI:

Cost of treatment = AUD2.0–0.2 million/1000 cases = 1.8 million/1000 cases = AUD1800/case
No. of deaths that will be prevented = 90–80 = 10 deaths/1000 cases treated
Marginal cost of TPA over SK = AUD1.8 million/10 lives = $180 000 per life saved

If one has a budget of only AUD 500 000, which drug should one use?

For SK:

No. cases that can be treated = 500 000/200 = 2500
No. lives that can be saved = (30/1000) x 2500 = 75

For TPA:

No. cases that can be treated = 500 000/2000 = 250
No. lives that can be saved = (40/1000) x 250 = 10

Conclusion

Although TPA is slightly more efficacious and saved marginally more lives, when cost was taken into account, more patients could be treated and more lives saved using SK. In other words, the extra cost of TPA over SK was so high ($180 000 per life saved) that with the limited budget available fewer people could be treated and lives saved, using TPA as compared to SK.

Sources: Fibrinolytic Therapy Trialists' Collaborative Group (1994); Aylward (1996)

ANNEX 4.1

Sources of information

Examples of primary literature sources

Websites that provide entire articles online, for example:

- The Iowa Drug Information System (http://www.silverplatter.com/catalog/idis.htm)
- Medline (http://www.nlm.nih.gov/databases/freemedl.html)

Peer-reviewed journals that publish original articles, for example:

- *American journal of health-systems pharmacy* (formerly the American journal of hospital pharmacy)
- *Annals of internal medicine*
- *British medical journal* (http://www.bmj.com)
- *Journal of the American Medical Association*
- *The Lancet* (http://www.thelancet.com)
- *New England journal of medicine*

Examples of secondary literature sources

Medical letters, newsletters or bulletins produced by national bodies responsible for monitoring drug efficacy, safety, and cost, for example:

- *Drug and therapeutics bulletin of the UK*, 2 Marylebone Road Street, London NW1 4DF, UK, email: dtb@which.net (http://www.which.net)
- *Medical letter of the USA*, 1000 Main Street, New Rochelle, New York 10801, USA, (http://www.medletter.com)
- *Prescrire international* (English summaries of *La Revue Prescrire*) (http://www.prescrire.org)
- *Australian prescriber* (http://www.Australianprescriber.com)

Peer review journals that publish review articles of the published literature, for example:

- *Journal watch* (http://www.massmed.org/)

Electronic databases that can be used to search for primary literature and provide abstracts, for example:

- Index Medicus
- Medline
- EMBASE
- Micromedex CD ROM
- International Pharmaceutical Abstracts (IPA)

Electronic databases that provide evidence-based evaluations, for example Cochrane Library abstracts (which are free) and evaluations.

Examples of tertiary literature sources

Textbooks and reference manuals on drug efficacy and safety, e.g:

- *AHSF drug information*, 1999, American Society of Health System Pharmacists, 7272 Wisconsin Ave, Bethesda, MD 20814.
- *British national formulary*, biannual, British Medical Association and Royal Pharmaceutical Society of Great Britain, BMJ Books, P.O. Box 295, London WC1H 9TE, UK, ISSN0260-535X, email: orders@bmjbookshop.com
- *Martindale: the complete drug reference*, 1999, Pharmaceutical Press, 1 Lambeth High St, London SE1 7JN, UK, ISBN: 0-85369-429X.
- *USP DI Drug information for health care providers*, Volumes 1, 2, and 3, 1996, USPC Board of Trustees, 12601 Twinbrook Parkway, Rockville, MD 20852, USA, ISBN: 0-913595-91-8.
- WHO, 2002, *WHO model formulary*, Department of Essential Drugs and Medicines Policy, WHO Geneva, ISBN: 92-4-154559-3, email: bookorders@who.int (http://www.who.int/medicines/organization/par/formulary.shtml).

International drug price lists, for example:

- *IDA price indicator*, International Dispensary Association, PO. Box 37098, 1030 AB Amsterdam, The Netherlands, email: info@ida.nl (http://www.ida.nl); tel: +31 20 40 33 051; fax: +31 20 40 31 854.
- *International drug price indicator guide*, annual publication by MSH in collaboration with WHO, 165 Allandale Road, Boston, MA 02130-3400, USA. Tel. +1 617 524 7799 Fax: +1 617 524 2825; email: bookstore@msh.org, (http://www.msh.org/publications, http://erc.msh.org and http://www.who.int/medicines/organization/par/ipc/drugpriceinfo.shtml)

Internet resources, for example:

- *Australian prescriber* (http://www.Australianprescriber.com)
- *British national formulary* (http://www.bnf.vhn.net)
- *British medical journal* (http://www.bmj.com)
- Biomail (http://biomail.sourceforge.net/biomail/) is a new search tool which periodically does a user-customized Medline search and sends the articles to the user's email address
- Centres for Disease Control and Prevention (CDC) Atlanta, USA, online information system (http://www.cdc.gov)
- Cochrane Collaboration (http://www.cochrane.org)
- Facts and comparisons – an Italian database website (http://www.burioni.it/script/rec.htm)
- Federal Drug Authority (FDA), USA, online information system (http://www.fda.gov/)
- Health InterNetwork Access to Research Initiative, which provides free online access to some journals for institutions in the poorest countries (http://www.healthinternetwork.org)
- Hirewire Press (http://Pstanford.edu)
- Internet browser searches, for example http://www.google.com or http://www.altavista.com
- International Society of Drug Bulletins (http://prn.usm.my/isdb.html)

- Liverpool School of Hygiene and Tropical Medicine website (http://www.liv.ac.uk) provides links to an number of journals, websites and databases
- Micromedex drug monographs, information from the United States Pharmacopeia (USP) (http://www.usp.org and www.micromedex.com/products)
- Medline (http://www.nlm.nih.gov)
- National Institute of Health (NIH) online information system: http://www.nih.gov
- PubMed Central (http://pubmedcentral.nih.gov)
- Satellife free information services to health professionals (http://www.healthnet.org)
- The free medical journal site (http://www.freemedicaljournals.com)
- *The Lancet* (http://thelancet.com)
- *The Lancet*'s experimental research archive in international health (http://www.thelancet.com/era)
- World Health Organization (http://www.who.int/medicines)
- WHO library site (http://www.who.int/hlt/virtuallibrary/English/subject.htm)
- WHO drug price information site (http://www.who.int/medicines/organization/par/ipc/drugpriceinfo.shtml)

ANNEX 4.2

Checklist to detect common problems encountered in articles

Adapted from Fowkes and Fulton (1991) and Bero and Cho (1994).

Checklist	Potential problems
Objectives	
Are the objectives stated in the abstract, introduction or methods?	A drug may be tested only against a placebo, or against a drug with poor past performance and not against the standard or most effective drug in its class.
Is sufficient information given about the disease outcomes and the effects of the drug studied, so that you may judge how clinically important they are?	Clinically unimportant outcomes may be used.
Methods	
Was a randomized controlled trial (RCT) done? — best design for efficacy Was a case control study done? — commonest design for safety	The study design may be insufficient to be able to ascribe observed differences to the new drug being tested.
Was the study blinded? If not, is this explicitly discussed? and are the confounders accounted for?	Study participants or investigators are not blinded, leading to possible bias in interpreting the results.
Is sufficient information given on the drugs used and the disease states treated in order to judge whether the study is relevant to your patient population?	Study patients may not be representative of the population that will take the drug. Often the patients in studies are fitter and have a more certain diagnosis and fewer concurrent diseases than the population who would take the drug.
Was the sample size of patients sufficient to detect significant differences in outcomes between intervention and control groups?	The number of patients may be too small to ensure any differences are not due to chance.
Were the inclusion and exclusion criteria of patients specified? Was the assignment of patients randomized? Were the control subjects appropriate?	Patients may not have been randomized to study and treatment groups so that patients treated with the new drug may not be similar to those treated with the comparator drug.
Is the drop-out rate of patients in the intervention and control groups reported? Were the rates the same? If not, is any explanation given for the different rates?	Patients randomized to take the new drug may not have completed the study so that side-effects or less effect of the drug may not be reported. Patients with more side-effects or less effect may be more likely to drop out.
How many dose regimes were compared for each drug? Were they equivalent?	Different drugs may be compared using fixed non-equivalent doses; the comparator drug may be under-dosed.
Review articles and meta-analysis (analysis across different RCT studies) — What criteria were used to find the articles? — How was the search done? — Which databases were used and were unpublished articles included? — Is there a description of how individual studies were appraised, and, if relevant, meta-analysis done?	Review articles and meta-analysis may be biased by which studies are included and which not, and how each study was appraised. Studies with negative results may have been excluded.

Checklist	Potential problems
Economic articles Are all the costs associated with drug treatment, including good and bad outcomes, described? (not just prices)	Economic articles may be biased due to incomplete reporting of all the costs associated with a drug treatment i.e. non-drug costs (for example equipment) and outcomes, including negative ones (for example side-effects).
Has discounting been used to reflect the costs of any future benefits or consequences in present day values?	Different discounting rates for drug costs and future benefits may be used to emphasize a drug's cost-effectiveness ratio.
Results	
What measures of outcome were used? Were any differences shown due to real differences between intervention and control groups or just due to chance from small sample size or by selecting a small subset of patients?	The presentation and analysis of data may be misleading. Differing efficacy can only be assessed by using established measures, for example relative or absolute risk reduction or number of patients needed to treat (see section 4.4).
For economic studies: What type of analysis was done? cost minimization? cost-effectiveness analysis? Has a sensitivity analysis been done?	Economic evaluation requires using standard analyses (see section 4.5).
Were the differences in clinical outcome between groups large, important and relevant as well as statistically significant?	The statistical significance of a trial may be valid but the clinical significance may be weak.
Were all recruited patients taken into account in the analysis? If patients who died or dropped out of the study are excluded from the analysis, there may be a bias towards greater efficacy.	Confounding variables may not have been adequately controlled so that any differences seen are due to the confounders not the new drug.
Conclusions	
Were the populations for which conclusions were drawn represented by the subjects in the study?	The conclusions may not agree with the results or may be extrapolated too widely.
Was there any discussion of whether the potential benefits were worth the potential harm? If not, maybe the likely benefits are not worth the risk.	There may be little discussion of safety in relation to efficacy.
Funding	
Is there a description of how the study was funded? What is the reputation of the authors, and are their affiliations described?	The study may have been funded by a drug company for their own product; often drug companies do not publish negative studies.
Is the study published in a peer-reviewed journal that is listed in *Index Medicus*, which covers all major reputable journals? Are references cited, and are they reputable?	Study may not be peer reviewed but published either in a 'throw-away' journal or in symposia proceedings; alternatively it may be published in a journal with less rigorous peer review.

5. Ensuring medicine safety and quality

Summary

A significant amount of harm to patients and wastage of resources is caused through the use of unsafe, poor-quality medicines. The DTC has a role to ensure that all medicines prescribed and dispensed to patients are safe and of good quality. This involves:

- monitoring and addressing medication errors
- ensuring medicine quality through ensuring good practices concerning procurement, storage and distribution and monitoring and addressing drug quality problems
- monitoring and addressing adverse drug reactions, which may be caused by the chemical entity itself or may be due to medication errors or poor drug quality.

These activities necessarily involve looking at the health system as a whole to identify practices and environmental problems that may be contributing to poor drug safety and quality.

5.1 The need for ensuring medicine safety and quality

Medicine safety problems are commonly caused by medication errors, poor quality, and certain drugs that are inherently unsafe (cytotoxic drugs, for example). Such safety problems are manifested through adverse drug reactions (ADRs), which may result in serious patient harm, extended hospital stay and large consumption of resources. A drug and therapeutics committee (DTC) has a role in ensuring that all medicines are prescribed, dispensed and administered to patients in as safe a way as possible, and that all medicines so given are, in themselves, safe and of adequate quality. Some assessment of safety can be made from the literature, as described in chapter 4 on assessing new medicines. However, there are three very important areas where the active involvement of a DTC can help to ensure the safe use of safe medicines that are of adequate quality:

- monitoring and addressing medication errors
- monitoring and ensuring drug quality
- monitoring and managing ADRs.

5.2 Monitoring and addressing medication errors

A medication error is any preventable event where a dose of medication that is received by a patient differs from what the prescriber has prescribed, or from hospital policy and procedures (AHSP 1999). These errors may result in therapeutic failure and adverse drug reactions as well as wasting resources. It has been estimated that medication errors cause 7000 deaths per year in the USA (Philips and Christenfeld 1998). In another study, 2% of inpatients in two teaching hospitals experienced preventable ADRs increasing the cost of their hospitalization by US$4700 per admission and the length of their stay by 4.6 days

(Bates et al. 1997). One of the functions of the DTC is to monitor and report on the occurrence of medication errors in order to ensure that they occur as rarely as as possible. The following are some of the possible errors that can occur either in the prescribing, dispensing or administration processes, and which should be monitored:

- prescribed medication not given
- administration of a drug that was not prescribed
- medicine given to the wrong patient
- wrong medicine or IV fluid administered
- wrong dose or strength given
- wrong dosage form given, for example eye drops instead of ointment
- wrong route of administration
- wrong rate of administration, for example IV infusion
- wrong time or frequency of administration
- medicine given for the wrong duration
- wrong preparation of a dose, for example incorrect dilution of a dose, not shaking a suspension
- incorrect administration technique, for example unsterile injection technique (see section 8.2) or incorrect installation of eye ointment
- medicine given to a patient with a known allergy.

Having a pharmacist or nurse, or another doctor or prescriber, review the prescriptions before the drugs are administered can prevent some of these errors. Whenever an error is identified, it must be documented and the prescriber or nurse administering the medication informed. **All errors should be compiled and a report presented monthly. It is important to do this in a non-confrontational manner without mentioning names of the doctor, nurse or pharmacist responsible for the errors**. The report should contain information about the number and type of errors, the type of staff reporting each error and the ward or department. The DTC should review all medication errors in order to (1) address individual incidents, and (2) look for patterns and trends in order to address health system, managerial and environmental problems that may be encouraging such errors. Table 5.1 shows a sample report of medication errors from a Zimbabwean hospital.

Common underlying problems that are associated with medication errors, and which the DTC could address, include:

- high staff workload and fatigue
- inexperienced and inadequately trained staff
- poor communication among health-care workers, including poor handwriting and verbal orders
- environmental factors, for example poor lighting, much noise, frequent interruptions
- increased number or quantity of drugs per patient
- frequency and complexity of calculations needed to prescribe, dispense or administer the drug
- large number of formulary medicines and dosage forms (such as injections) that are associated with more errors

Table 5.1 **Medication errors report for September 1999 in a Zimbabwean hospital**

Type	Ward	Brief description	Reporter	Total
A	C6	heparin 15000 u/100 ml given instead of 10000 u/100 ml	Nurse	
A	B4	ofloxacin 200 mg tablet given instead of 400 mg tablet	Doctor	
A	A4	theophylline 5 mg/kg loading dose given instead of 6 mg/kg	Pharmacist	
		All errors of dose or strength		3 (42.9%)
B	A2	amoxicillin given 4 times instead of 3 times daily	Nurse	
B	C1	furosemide prescribed every 4 hours but given every 6 hours	Nurse	
B	B3	potassium chloride prescribed every 8 hours but charted 1000hrs, 1600hrs and 2100hrs	Pharmacist	
		All errors of time or frequency		3 (42.9%)
C	A4	chlorpromazine given instead of chlorpropamide	Pharmacist	
		All errors of actual drug		1 (14.2%)

Source: *Zimbabwe DTC manual* (1999).
Key: A, wrong dose or strength; B, wrong time or frequency; C, wrong drug.

- confusing drug nomenclature, packaging or labelling
- lack of effective drug policies and procedures.

Some ways of preventing medication errors, particularly in hospitals, include:

- establishing a consensus group of physicians, nurses and pharmacists to select best practices
- introducing a punishment-free system to collect and record information about medication errors
- developing written procedures with guidelines and checklists for the administration of intravenous fluids and high-risk drugs such as insulin, heparin and narcotics
- developing standardized times to administer medicines and a policy to do so only when patients are on the wards
- requiring that a patient's identity be confirmed before administering a drug
- allowing verbal or telephone orders only in an emergency
- requiring legible handwriting and complete spelling of a drug name
- requiring the use of standardized notation
- dose units written in one way only, for example 'mcg' not 'µg' or 'g' not 'gm'
- use of leading zeros for values less than 1 (0.2 instead of.2) and avoidance of trailing zeros for values more than 1 (2 instead of 2.0)
- requiring that the route of administration and the complete directions (for example 'daily' not 'OD') be written on all drug orders (prescriptions)
- requiring that prescribers write generic and brand names for medicines with 'look-alike' or 'sound-alike' names.

5.3 Monitoring and ensuring medicine quality

Poor quality of medicines undermines health care and is unfortunately quite common in many countries. Accepted quality standards for testing drugs are published in various pharmacopoeias, for example the US, British, European or International Pharmacopoeias. Quality criteria are purity, potency, uniformity of dosage form, bioavailability and stability. All these aspects of quality may be affected by the manufacturing process, packaging, storage and other factors. Poor quality may result in lack of therapeutic effect, and cause adverse or toxic reactions; these in turn may result in harm to patients (through prolonged or drug-induced illness), as well as waste of limited resources.

Product quality is ensured through adherence to a quality assurance system. Brief definitions are given below (MSH 1997, chapter 18 on 'Quality Assurance for Drug Procurement' and chapter 24 on 'Drug Management for Health Facilities'; WHO 1999a).

- **Quality assurance** is the sum of the activities and responsibilities intended to ensure that medicines reaching patients are safe, effective and acceptable to the patient.
- **Good manufacturing practices (GMP)** are part of quality assurance and should ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use and required by drug regulatory authorities.
- **Quality control** is the part of GMP where drug samples are tested against specific quality standards. Laboratory testing of drug samples is done by the manufacturer during the process of manufacture (resulting in a certificate of analysis for each batch). Testing may be carried out during the licensing process by the national drug regulatory authority. Testing may also be done by the purchaser (or DTC) after receipt of medicines. Non-compliant, poor-quality samples found at this stage may result from a variety of causes such as poor manufacture, storage or handling.

Inadequate quality of medicines not only undermines health care in general, through lack of therapeutic effect and increased adverse reactions, but also other aspects of medicines policy. For example, a DTC may be unable to implement a generic substitution policy because it cannot distinguish between good-quality and poor-quality generic products and therefore prescribers believe all these products to be of poor quality. Many bodies are involved in drug quality assurance – drug licensing authorities, regulatory bodies, enforcement authorities and inspectorates, drug procurement offices, pharmacies and prescribers (by reporting on non-effectiveness). DTCs can help to ensure drug quality through coordination of all the various actors within health facilities and liaison with manufacturers and drug regulatory bodies.

Efficient management of the hospital medicine system will help to ensure the availability of medicines of adequate quality as well as containing costs. The DTC should work closely with the hospital pharmacy to provide guidance and promote recommended principles in procurement, storage and distribution. Where there are no existing policies and guidelines on supply management, the DTC should initiate action and give advice to the pharmacy. Pharmacists are vital in ensuring good drug quality and supply management; they are also the partners of prescribers in ensuring that patients receive safe and effective drug therapy. However, in many developing countries, pharmacists often have rather low status. It is therefore important that the image and status of the pharmacy and the pharmacist be raised when human resource development is considered.

5.3.1 Role of the DTC in procurement

Procurement practices can have a significant bearing on drug quality. The DTC should ensure that the practices followed by the responsible department will ensure adequate

drug quality. The DTC should not spend committee time and meetings in deciding order lists, nor should DTC members generally be on tender committees assessing bids to supply drugs. However, a DTC should monitor and ensure implementation of good procurement procedures. In some hospitals this may mean the DTC has to reassess and identify the limits of its role. The DTC must be represented in the preparation of the annual hospital budget, including review and allocation of the drug budget. Criteria for good procurement practices have been agreed by WHO, UNICEF, UNFPA and the World Bank (WHO/UNICEF/UNFPA/WB 1999) and are summarized in box 5.1 in the context of hospital practices.

5.3.2 Role of the DTC in medicine distribution and storage

The quality of medicines can be adversely affected by poor storage and distribution. The DTC has a role in ensuring that the practices followed by the responsible department are consistent with those that ensure the highest possible drug quality. In some situations this may mean that the DTC must be able to assist the pharmacy in initiating and monitoring an adequate system for drug storage and distribution. Good storage and distribution practices are summarized in box 5.2.

BOX 5.1 GOOD PROCUREMENT PRACTICES

Efficient transparent management

- Divide procurement functions and responsibilities (selection, quantification, product specification, pre-selection from suppliers and adjudication of tenders), among different offices, committees and individuals to ensure that no one individual is dealing with all activities and thus susceptible to undue external influences. The DTC should be responsible for selection and product specification, and the procurement department for the other functions.
- Follow explicit documented procedures for adjudicating tenders and awarding procurement contracts. The procurement department should do this and should regularly report to the DTC and senior management, and undergo external audit annually.

Drug selection and quantification

- Base procurement on the formulary list, using generic or International Nonproprietary Names (INN). The DTC should decide the formulary list and approve purchase of non-formulary drugs.
- Select formulary drugs carefully to ensure safety and efficacy. This includes choosing appropriate dosage forms, preparations and packaging and defining the specifications of the products to be purchased; for example, theophylline elixirs for children should not contain alcohol.
- Use the method of quantification best suited to the available data – morbidity method if morbidity data are available and standard treatment guidelines (STGs) are followed, or consumption method if there are no morbidity data and STGs are not followed. Adjustments may have to be made cautiously if there is not enough budget to procure all the medicines needed (see point below).
- Use VEN analysis (see section 6.2.3) to identify the most essential medicines, especially if there is insufficient budget to finance all medicine needs. The DTC should assist the procurement group to do this once each department has submitted the yearly quantification of medicine needs.

Financing and competition

- Buy in bulk if possible. DTCs of small hospitals can collaborate with other hospitals and recommend that bulk procurement be done jointly to get good value for money.

Continued

BOX 5.1 *CONTINUED*

- Agree a regular procurement schedule and decide criteria for emergency purchase in circumstances where it is absolutely indispensable to prevent immediate danger to life.
- Purchase only from the supplier who holds the current contract as decided through the competitive tender adjudication process to ensure the lowest possible purchase price.

Supplier selection and quality assurance

- Procure only registered products from reliable, licensed suppliers and manufacturers that comply with GMP and have good records of performance, to ensure that medicines procured meet the required standard of quality. The qualification of suppliers can be checked through networking with the national drug regulatory body and other agencies, obtaining all appropriate certification and, if necessary, laboratory testing of received products. Some purchasers have negotiated with manufacturers to pay for quality testing at a laboratory of the purchaser's choice. Suppliers who do not have permanent addresses or who are not prepared for visits to their premises without prior notice are unlikely to be reliable.
- Only accept medicines with the appropriate documentation, including:
  - a certificate of analysis issued by the manufacturer (batch certificate)
  - for imported medicines, a WHO-type certificates issued by the drug regulatory authorities of the exporting country
  - detailed product specifications.
- Ensure quality through the inclusion of certain pre-tendering criteria, for example specifying a minimum shelf-life, or insisting manufacturers have a minimum turnover or proof of GMP compliance.
- Find out from various sources (such as regulatory bodies) whether a generic product is bioequivalent to the brand product. If it is not, efficacy can only be established by a clinical trial. If possible, ask the manufacturers to produce evidence of bioequivalence.

Adapted from WHO/UNICEF/UNFPA/WB (1999)

5.3.3 Monitoring and analysing medicine quality problems

A very important role of the DTC is to monitor and analyse all reports of inadequate medicine quality. The problem may present in the following ways:

- visual deterioration of the product as reported by health staff, for example discolouration, fragmentation, leakage, smell
- lack of therapeutic effect
- ADRs.

Once a problem has been reported, it should be investigated (see section 5.4.3) to see if the problem is one of manufacture (including counterfeit), storage, distribution, administration or use. This may involve the following steps:

- Confirming the exact nature of the problem.
- Visually inspecting the product, including the expiry date, the packaging and the labelling.
- Eliciting information concerning the product's procurement, storage and distribution.
- Observing how the product is administered, for example injection technique, dispensing process, interviewing the patient if necessary to check on compliance.

BOX 5.2 GOOD STORAGE AND DISTRIBUTION PRACTICES

- Documented drug distribution and control procedures are in place, for example
  - — procedures for inventory control and management
  - — minimum and maximum safety stock levels
  - — visual inspection of all medicines, their packaging and labelling, on arrival at the facility.
- Facilities/departments use pre-defined re-ordering quantities (or methods for calculating drug quantities) for drug orders from the store to avoid shortage and stock-outs.
- Storage conditions should be adequate to maintain the quality of the medicines and free from factors that can cause the deterioration of drug products:
  - — Appropriate medicines only are stocked in hospital patient care areas (VEN analysis important).
  - — Manufacturers' storage instructions are followed; if no special instructions are given, use 'normal storage conditions' (temperature 15–25 °C).
  - — Storage areas are clean and dry.
  - — Medicines are arranged either alphabetically or by therapeutic category.
  - — Repackaging is avoided wherever possible and done only by staff trained to do it; likewise, pre-packaged drugs for individual patients are prepared only by trained staff.
- The expiry date is one important assurance of drug quality. Drugs should be stored according to a first-expiry, first-out policy and there must be a mechanism to dispose of expired medicines. For medicines with the same expiry date, a first-in first-out policy should be followed.
- Narcotics and other controlled drugs should be stored in a separate area locked by two keys, each key controlled by a different person.
- Transport is speedy and conditions are sufficient to maintain medicine quality. In particular, cold-chain procedures should be documented and strictly enforced.
- Appropriate dispensing procedures are in place, for example containers, labelling, patient information and counselling.

- Observing how the patient is managed. For example, when dealing with a complaint that a hypoglycaemic drug is not effective, one might do a patient chart audit to check (1) how the drug was being prescribed, and (2) what was the evidence about poor blood sugar control. A prescriber could not claim that a drug was ineffective if blood or urinary sugar was not monitored.
- Analysis of the product. A product may be analysed first using basic (less expensive) tests, which can screen out counterfeit medicines or those of very poor quality. If the product passes such a screen, but has been the subject of complaints about quality, it should be subjected to further full pharmacopoeial (more expensive) tests in a properly equipped laboratory. See annex 5.1 for basic tests.
- Reporting to the national regulatory authority drug products found to be of poor quality on receipt from the manufacturer or supplier.

Quality problems are likely to be more serious in medicines that are inherently unstable or have a narrow therapeutic index (narrow range for effective serum levels). These medicines are listed in table 5.2. The same drug product produced by different manufacturers may have differences in bioavailability and therefore be non-bioequivalent. It is much harder

to ensure bioequivalence between products where the drug has a narrow therapeutic index. An additional quality factor to consider in drug selection and management is the varying stability of different forms of oral medicines. Generally speaking, solid forms are more stable than liquid forms, especially in tropical or humid conditions. Syrups and injections that are in powder form are more stable than those in liquid form.

Decreasing stability of oral drugs: ⟶

tablets capsules suspensions syrups and solutions

Table 5.2 **Drugs with known potential bioavailability or stability problems**

Bioavailability problems			Stability problems
aminophylline	furosemide	nitrofurantoin	acetylsalicylic acid tablets
ampicillin	glibenclamide	oestrogens	amoxycillin tablets
carbamezepine	glyceryl trinitrate	phenytoin	ampicillin tablets
chloramphenicol	griseofulvin	prednisolone	penicillin V tablets
chloroquine	hydrochlorthiazide	quinidine	retinol tablets
chlorpromazine	iron sulfate	rifampicin	paracetamol liquid
digitoxin	isosorbide dinitrate	spironolactone	penicillin V suspension
dihydroergotamine	levodopa	theophylline	ergometrine injection
ergotamine	methotrexate	L-thyroxine	methylergometrine injection
erythromycin	methyldopa	warfarin	

Source: *Managing Drug Supply* (MSH 1997), p.273.

5.4 Safety of medicines

The safety of medicines is critically important to health care. A DTC may have a significant impact on preventing and managing drug safety problems through:

- assessing the literature on safety issues of new medicines proposed for the formulary (see chapter 4)
- preventing the occurrence of ADRs by ensuring that patients are carefully evaluated before medicines are prescribed and ensuring staff are trained accordingly (see section 7.2)
- implementing systems to monitor the occurrence of ADRs, which includes the regular review of ADR reports
- evaluating suspected ADRs
- reporting ADRs to regulatory authorities and manufacturers
- monitoring and investigating medication errors (see section 5.1)
- monitoring and investigating problems of medicine quality (see section 5.2).

5.4.1 Definitions

The following definitions were adopted by national centres participating in the WHO International Drug Monitoring Programme in September 1991. Further information can be obtained from the WHO Collaborating Centre at Uppsala (http://www.who-umc.org).

Side-effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug. Such effects may be either positive or negative.

Adverse event or experience

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction (ADR)

A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. An **unexpected** adverse reaction refers to a reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug. A **serious** adverse reaction is any medical occurrence that at any dose normally used in humans:

- results in death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is life-threatening.

Causality assessment of suspected adverse reactions

This refers to the likelihood that a medicine has caused an adverse event, and is described further in box 5.3.

- **Certain causality** is where a clinical event (including a laboratory test abnormality) occurs in a plausible time relationship to drug administration, and cannot be explained by concurrent disease or other drugs or chemicals. A plausible (expected) clinical response to withdrawal of the medicine must be demonstrated and, if possible, the clinical response to restarting the medicine should also be demonstrated.
- **Probable or likely causality** is where a clinical event occurs with a reasonable time sequence to drug administration, and is unlikely to be due to any concurrent disease or other drugs or chemicals. A plausible clinical response to withdrawal of the medicine, but not to restarting the medicine, must be demonstrated.
- **Possible causality** is where a clinical event occurs with a reasonable time sequence to drug administration, but which could be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

5.4.2 Adverse drug reactions (ADRs)

ADRs are a serious problem with increasing incidence, as more drugs become available and more people become exposed to them. In the USA, a review of prospective studies showed that in 1994 hospitalized patients had 2.2 million adverse drug reactions (6.7% incidence) and this resulted in 106 000 fatalities. (Lazarou et al. 1998). Box 5.3 shows the different types of ADRs.

BOX 5.3 CLASSIFICATION OF ADRS

Type A reactions

These are an exaggerated but otherwise normal pharmacological response to the effects of the medicine given in therapeutic dose. These reactions cause significant morbidity but are rarely severe. Examples include:

- pharmacodynamic, for example bronchospasm with beta-blocker administration
- toxic, for example absolute or relative overdosing of aminoglycosides causing deafness
- withdrawal syndrome or rebound effect, for example spontaneous rise in blood pressure with clonidine discontinuation.

Type B reactions

These are bizarre and unpredictable with no relation to dose and are often allergic in nature. They are often severe and cause high mortality. Examples include:

- idiosyncratic reactions, for example irreversible aplastic anaemia caused by chloramphenicol
- anaphylactic reactions, for example anaphylactic shock with penicillin
- drug-induced diseases, for example antibiotic-associated colitis.

Adverse events as a result of drug interactions

These may be of all degrees of severity and type, for example

- reduced absorption of tetracycline if administered with ferrous salts
- reduced anticonvulsant effects of phenytoin if administered with some antimalarials such as pyrimethamine
- serious and severe rise in blood pressure following concurrent administration of monoamine oxidase inhibitor antidepressants with tricyclic antidepressants or some antipsychotics.

All new medicines undergo a significant amount of testing and evaluation before marketing to ensure the product is not only effective, but also safe. There are no drugs that are free of side-effects or adverse reactions. Though many products have an extremely low incidence, some have a relatively high incidence of adverse reactions that may result in death. Even the most effective medicines, prescribed by the most careful practitioners, have a certain amount of risk attached. For example, oral polio vaccine has nearly eliminated the disease worldwide but can, very rarely, cause cases of polio. Thus, every drug has risks and benefits, which must be balanced, and which may depend on many factors such as the condition(s) being treated, other problems, age, gender, etc.

Although all medicines undergo mandatory clinical trials before marketing in order to establish efficacy, safety, and quality, such trials will only uncover the commonest ADRs (>1% incidence). Less common ADRs (<1% incidence) will only be discovered through post-market surveillance of much larger numbers of patients taking the drug. Such post-market surveillance relies mostly on spontaneous reporting by physicians, pharmacists and patients. Often the national regulatory body is responsible for monitoring ADRs at the national level. If this authority identifies a serious drug safety issue, it may organize recall of the drug, or revision of the package insert, or distribution of letters to doctors explaining the safety issues. What is done will depend on the nature and seriousness of the problem. However, many ADRs are due not to inherently unsafe drugs but to problems of use or quality, which can be corrected locally.

The DTC should implement a system to monitor, track, investigate and report adverse reactions to drugs and vaccines within their hospital and/or health facility. Any serious

findings should be reported to the national monitoring centre, which is often the drug regulatory body. ADRs are monitored not just for the sake of reporting and statistics, but more importantly, to encourage safer use of medicines by minimizing unsafe use of all drugs and avoiding the use of unsafe medicines. The DTC should therefore investigate all serious ADRs in depth and collate and report on all ADRs in order to see how they can be avoided and risk factors for their occurrence reduced. Any ADR monitoring system should include, as a minimum:

- reporting of an ADR to the DTC on standard forms (see annex 5.2)
- investigation and analysis of reports by a selected DTC member
- discussion and evaluation of reports by the DTC on a regular schedule (quarterly) and report to medical staff
- reporting to manufacturers and national regulatory authorities of all events thought to be ADRs (and not known side-effects).

5.4.3 Assessing and managing spontaneous ADR reports

An important part of monitoring ADRs is to process and analyse spontaneous ADR case reports arising from patients and medical providers. These spontaneous reports may be difficult to interpret and to assign causality.

Common problems include the following:

- A generic drug is alleged to cause an ADR whereas the brand named product does not.
- A brand named product is alleged to cause more side-effects than another branded product.
- An antibiotic suspension causes a reaction and it is unclear whether the antibiotic is responsible or one of the components of the suspension, i.e. a dye or other excipient in the suspension.
- An injectable product causes a reaction and it is unclear if the causative agent is the active ingredient, or the preservative or some other agent in the solvent, or the injection technique.
- A patient is on several medicines when a new adverse event is reported and assigning causality is difficult because any of the medicines could be the cause.
- The patient has co-morbidity that may have a bearing on the medicine and suspected ADR.

ADRs should be assessed and managed in three steps, as described below; an example is shown in box 5.4.

STEP 1 Evaluate the nature of the ADR

- Obtain a detailed history of the patient including current health status, current drug therapy, past medical history. Use an ADR reporting form to organize reporting (annex 5.2).
- Establish and document the clinical syndrome described by checking the description with health workers and looking up the clinical description and suspected medicine(s) in the literature.
- Classify severity of the reaction:

  — **severe**: fatal or life threatening

BOX 5.4 INVESTIGATION OF AN OUTBREAK OF ADRS IN PANAMA

A DTC in Panama served 11 clinics and a hospital. Recently a different brand of procaine penicillin injection had been purchased and distributed. Shortly after introduction of the new brand of procaine penicillin, one clinic reported to the DTC that within a short period of time there had been an unusually high number of ADRs following intramuscular injection of penicillin. The nurses were alarmed, refused to use the new product and demanded to change back to the old brand of penicillin. The adverse event was described as an adult patient suddenly (within seconds of the injection) experiencing feelings of doom, anxiety and faintness, necessitating lying down. Patients were reported to be pale, but with normal or slightly high blood pressure. The nurses immediately gave diphenhydramine (intravenous or intramuscular) for a suspected anaphylactic reaction to penicillin. After 10–15 minutes the patients would completely recover and leave the clinic unassisted.

A DTC member was assigned to investigate the ADR outbreak and the issue was dealt with as follows:

- The clinical syndrome described was looked up in the literature and found to be consistent with Hoigné syndrome or pseudo-allergy to penicillin caused by the procaine component of the injection when accidentally injected intravenously. Diphenhydramine was thought to be inappropriate treatment for either this reaction to procaine or any potential anaphylactic allergic reaction (where adrenaline was the recommended treatment).
- Using the number of penicillin-related ADR events reported in the clinic injection rooms and the number of procaine penicillin doses used, an event rate was calculated for each health facility for a fixed time period. This revealed that the rate of procaine penicillin-related ADRs in two clinics was double the rate occurring in the other clinics, and that the two affected clinics had a relatively high workload. Although one clinic had noticed and complained about the increased rate of ADRs, the other clinic had not noticed the problem before the investigation.
- The DTC staff member visited the two clinics with higher event rates, interviewed the nurses and observed the giving of injections. The nursing assistants were observed to use less water than required to reconstitute the injections. The DTC concluded that the accidental intravenous injection of more concentrated procaine was accounting for the ADRs.
- DTC staff discussed the findings and conclusions of the investigation with the nursing staff concerned, who reviewed how to prepare and give procaine penicillin injections. The nurses agreed to continue using the new brand of procaine penicillin injection. The DTC also discouraged the use of diphenhydramine for treatment of this clinical syndrome as it was not an allergic reaction.

After this intervention, the DTC again measured the recorded event rates and found that the ADR rate had decreased in the two affected clinics and was similar across all clinics.

Source: David Lee, Management Sciences for Health. Personal communication

  - — **moderate:** requires antidote, medical procedure, or hospitalization
  - — **mild:** symptoms requiring only the discontinuation of drug therapy
  - — **incidental:** very mild symptoms where the patient can choose whether to continue drug therapy or not
- Assess the likelihood of the suspected medicine being the cause of the ADR. This may be done using the definitions of causality (section 5.4.1). An alternative method is to use the Naranjo algorithm (see annex 5.3). This algorithm asks specific questions (based on the same definitions of causality) and scores the answers. Individual scores are then added up and the total score used to give some indication of the likelihood that an ADR was caused by the suspected medicine.

STEP 2 Establish the cause of the ADRs

- Confirm the clinical syndrome constituting the ADR to be investigated.

- Inspect the suspect medicine visually and check its procurement, storage and expiry date.
- Calculate the rate of ADRs occurring in different departments or clinics.
- Check whether there are any other differences between the departments or clinics showing high and low rates of ADRs to a particular medicine.
- Visit the departments or clinics with the highest rates of adverse drug reaction to observe how the suspect drug is being prescribed, dispensed and administered; this may require carrying out a drug utilization review (section 6.5) or observing the dispensing or administration processes.
- Contact other agencies, hospitals or the regulatory authorities to see if others have experienced similar ADRs, and if necessary or possible send the drug for quality testing.

STEP 3 Possible DTC action after ADR evaluation

Possible actions will depend on what the cause of the ADR is and may involve any or all of:

- reporting to the national drug authority and/or manufacturer
- implementing new prescribing procedures including restrictions
- educating prescribers if needed
- changing the formulary, if necessary, to obtain a drug of improved safety; this may mean substituting a drug that is absolutely safer or one that is easier to use by staff
- adapting the STG or formulary manual if necessary; either in terms of which medicines are recommended for the formulary, or what recommendations are made concerning how and when a formulary medicine should be used
- educating patients if necessary
- following up the rate of ADRs after action has been taken to reduce the ADRs to ascertain whether the DTC action has been successful.

5.4.4 Preventing ADRs

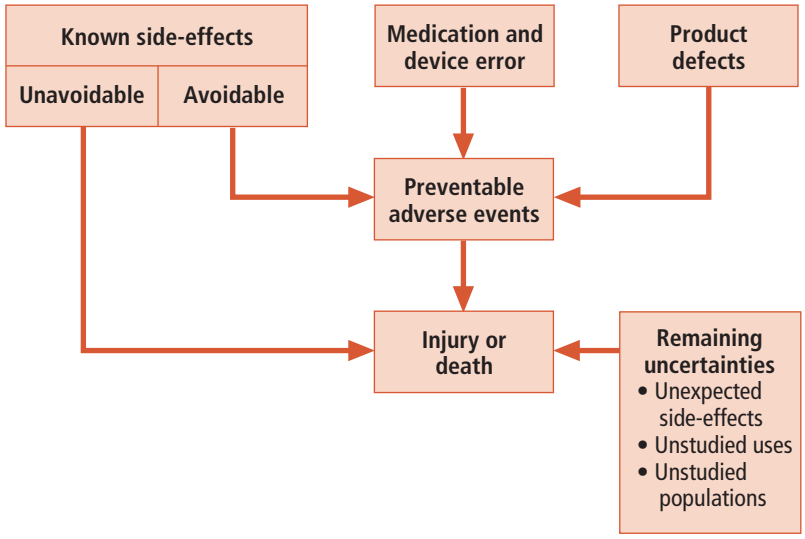
Prevention of ADRs is possible, and indeed necessary! Studies have shown that over 50% of adverse drug reactions may be preventable. Most ADRs are related to the prescribing of an incorrect dose or the administration of a drug to a patient with a known allergy.

Many ADRs could be avoided if the relevant health worker asked specific questions before prescribing and/or dispensing a drug, as shown in box 5.5.

The DTC can do the following things to help promote safety and limit the occurrence of ADRs:

- Encourage ADR reporting (and introduce it if it is not already in place).
- Educate staff about ADRs through in-service education, drug information bulletins and reports of collected adverse events.
- Identify drugs on the formulary that are 'high risk' and monitor their use closely (examples include aminoglycosides such as gentamicin, antineoplastics, digoxin, heparin, warfarin).
- Identify 'high risk' patient populations and monitor their treatment closely. Such patients include pregnant women, breast-feeding women, elderly people, children and patients with renal or liver dysfunction.
- Review ADR reports regularly and inform professional staff of the incidence and impact of ADRs in the region.

Figure 5.1 **Preventing ADRs**



BOX 5.5 QUESTIONS TO ASK BEFORE PRESCRIBING AND/OR DISPENSING A MEDICINE

- Is this the correct medicine for the patient's clinical condition?
- Is this the correct dose, route and interval?
- Has the patient had the appropriate laboratory test ordered and evaluated?
- Does the patient have any medical or physical conditions that would affect the pharmacokinetic aspects of the medicine?
- Does the patient have an allergy to this medication or a similar one?
- Is the patient on another drug (or herbal product) that would cause a significant drug interaction?
- Is the drug being prescribed a 'high risk' drug for producing ADRs (aminoglycosides, digoxin, warfarin, heparin, antineoplastics)? Such drugs require special precautions such as increased monitoring of the patient by the prescriber or increased laboratory monitoring (for example blood counts, drug levels, urea and electrolytes).
- Is the medicine date-expired?
- Does the drug show any visual deterioration, for example discolouration?
- Is the injection equipment sterile?

- Review medication error reports to take steps to control and limit these events.
- Undertake prescription audits and drug utilization evaluations (see section 6.5) in order to identify prescribing errors and take corrective action.
- Review product quality complaints and take necessary action to manage quality problems with the procurement department.
- Change the formulary or standard treatment guidelines where necessary for significant or recurring problems with adverse drug reactions.

ANNEX 5.1

Basic analytical medicine tests

The objective of basic tests is to provide a simple analytical method that is readily applicable, in the absence of a fully equipped laboratory, for verifying the identity of a medicine and whether there has been any gross degradation. Basic tests can never, under any circumstances, replace the requirements of the pharmaceutical monographs which give better assurance of quality.

Basic analytical tests may be done by trained pharmacy assistants in inexpensive, relatively low-tech laboratories, which could be run by the pharmacy departments in big hospitals. The minimum equipment needed for such a laboratory includes:

- An analytical balance that can measure weights of 50–200 g to within 1 decimal place of a milligram, and weights under 50 g to within 2 decimal places of a milligram).
- At least 50 chemical reagents (solid, liquid, gas), reference substances, chemical indicators, and solvents (to dissolve the reagents).
- Glassware, for example burettes, beakers and pipettes with a standardized scale.
- A recent copy of one of the major pharmacopoeias – British, US, European or International (WHO 1979, 1981, 1988b, 1994c, 2003) – which contain the quality specifications for medicines.

Even if a hospital does not have access to a laboratory, it is important that the DTC understands what tests are available in order to investigate drug quality issues and to understand pharmaceutical manufacturer documentation.

The basic screening tests should be done on at least 10 samples (tablets, capsules, etc.) of the drug and the result of each test compared against pharmacopoeial or national regulatory body standards. Tests consist of:

- Identification of the active ingredient through reactions of chemicals to produce colour or other changes or through thin layer chromatography.
- Assay to test for quantity, which is done by burette titration and requires a precise balance.
- Disintegration tests of the tablets or capsules in water or 0.1 normal solution of hydrochloric acid at 37°C (simulating gastric acid). The time taken for a tablet (or capsule) to disintegrate is measured and compared against pharmacopoeial standards; for most compounds disintegration should occur within 30 minutes.
- Homogeneity or consistency tests where the weights of different tablets (or capsules) of the same drug are compared and the range of weights compared with pharmacopoeial or other national standards.

Basic screening tests are described in WHO documents (WHO 1986, 1991, 1998). Bio-availability and bioequivalence can only be ascertained through very much more complex analytical tests.

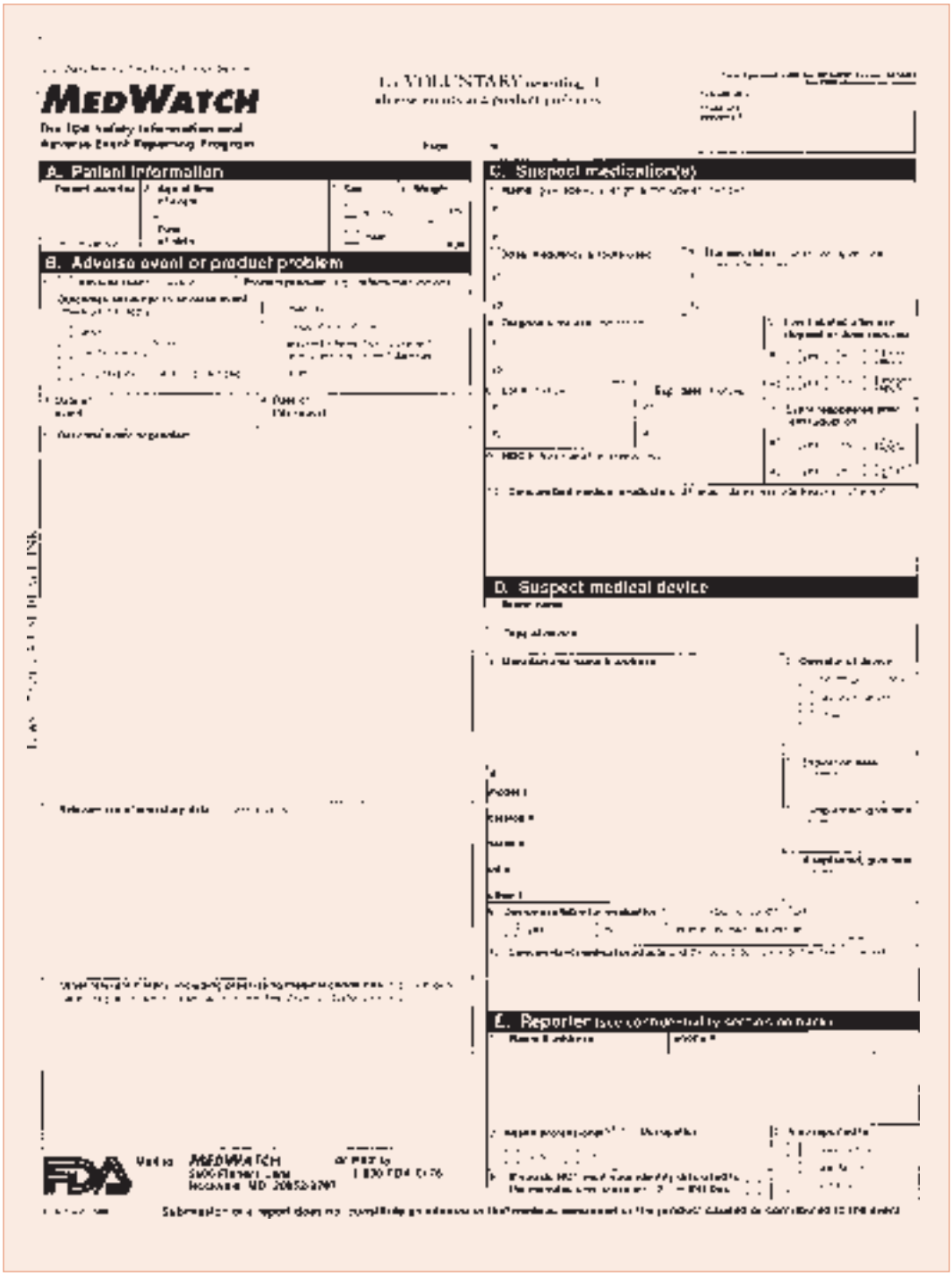
ANNEX 5.2

Examples of ADR reporting forms

A standard ADR report form for hospital and primary care clinic use only

Patient and reaction information		Comments
Date:	Chart number:	
Name:	Date of birth:	
Physician:	Ward/OPD:	
Drug:	Dose:	
Date drug started:	Date of reaction:	
Diagnosis for use (Indications):		
Relevant medical history and concurrent drug therapy:		
Description of ADR: (use reverse side if necessary)	1. 2. 3. 4.	
Outcomes attributed to ADR:	1. 2. 3. 4.	
Probability of reaction	Naranjo Score (see annex 5.3)	
Severity code	Severe Moderate Minor Incidental	
DTC action Mark patient's chart Discuss with prescriber Add to database Report to national drug authority Report to manufacturer	 Yes No Yes No Yes No Yes No Yes No	
Reported initiated by:	Date report initiated:	

ADR report form for the US Department of Health and Human Services Food and Drug Administration



MEDWATCH

A. Patient information

B. Adverse event or product problem

C. Suspect medication(s)

D. Suspect medical device

E. Reporter

FDA

MEDWATCH
5600 Fishers Lane
Rockville MD 20852-9787

1 800 FDA 1088

ADR report form for the US Department of Health and Human Services Food and Drug Administration *(continued)*

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

Report product problems –

Report SERIOUS adverse events. An event is serious when the patient outcome is:

Report even if:

How to report:

Confidentiality:

If your report involves a serious adverse event with a device

Important numbers:

To Report via the Internet:

Please Use Address Provided Below – Just Fold In Thirds, Tape and Mail

Department of Health and Human Services

Official Business

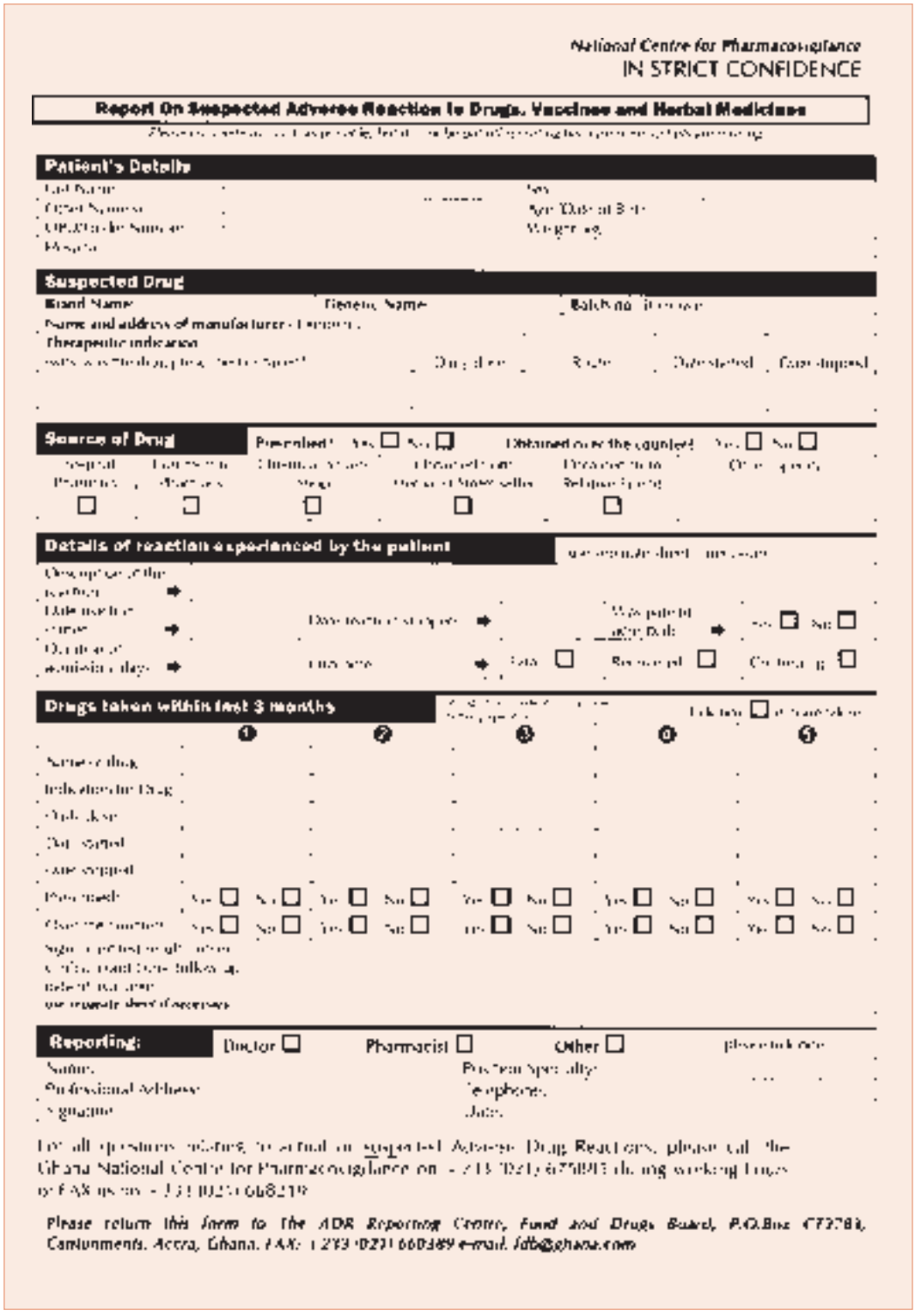
BUSINESS REPLY MAIL

FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE, MD

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

ADR report form for the National Centre for Pharmacovigilance in Ghana



National Centre for Pharmacovigilance
IN STRICT CONFIDENCE

Report On Suspected Adverse Reaction to Drugs, Vaccines and Herbal Medicines

Patient's Details

Suspected Drug

Source of Drug

Details of reaction experienced by the patient

Drugs taken within last 3 months

Reporting: Doctor ☐ Pharmacist ☐ Other ☐

For all questions relating to suspected Adverse Drug Reactions, please call the Ghana National Centre for Pharmacovigilance on [illegible] during working hours or FAX us on [illegible]

Please return this form to the ADR Reporting Centre, Food and Drugs Board, P.O.Box CT2783, Cantonments, Accra, Ghana. FAX: [illegible] e-mail: fdb@ghana.com

ANNEX 5.3

Naranjo algorithm for assessing the causality of an ADR

Question	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	–1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	–1	0
Are there alternative causes (other than the drug) that could solely have caused the reaction?	–1	+2	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total score			

Total score categories are defined as follows:

ADR is: certain > 9; probable 5–8; possible 1–4; unlikely 0.

Source: MSH (1996.)

6. Tools to investigate the use of medicines

Summary

The first step to addressing problems of irrational use of medicines is to measure the problem, analyse it and understand the causes underlying it. There are four main methods, all of which should be regularly used by DTCs.

- **Aggregate data methods** involve data that do not relate to individual patients and can be collected relatively easily. Methods such as ABC analysis, VEN analysis and DDD methodology are used to identify broad problem areas in drug use.
- **Drug indicators studies** involve collecting data at the level of the individual patient but do not usually include sufficient information to make judgements about drug appropriateness for diagnosis. Such data can be collected by non-prescribers and can be used to identify problem areas in medicine use and patient care, and evaluate interventions designed to correct the problems identified.
- **Qualitative methods** such as focus group discussion, in-depth interview, structured observation and structured questionnaires are useful for identifying why drug use problems occur.
- **Drug use evaluation** is a system of ongoing criteria-based evaluation of drug use that will help to ensure appropriate use at the individual patient level. This method involves the detailed analysis of individual patient data.

6.1 Stepwise approach to investigating the use of medicines

Medicines have been used irrationally for as long as they have been available; this reduces quality of care, wastes resources and may cause harm to patients. The first step to improving drug use is to investigate what kinds of problems there are and the extent to which they occur. Unless drug use is investigated, measured and documented, it is impossible to evaluate the effectiveness of interventions to promote rational use. This chapter describes a number of methods or tools to investigate drug use. It is up to the reader to choose the combination of methods most suited to the type of problem to be investigated and the type of data available.

STEP 1 General investigation to identify problem areas

Initial investigation should identify broad areas of inappropriate use of medicines. There are two main ways of doing this:

- **Aggregate data methods** (section 6.2) use data that are not collected at the individual patient level; such data are often routinely available for purposes other than investigating drug use, for example stock records. Aggregate data give an overview of drug use, which is useful in managing the formulary list.

- **Indicator study methods** (section 6.3) use data which are collected at the individual patient level, for example prescriptions or patient–provider interactions. Indicator study data are collected specifically to investigate medicine use, but do not include sufficient information to make individual judgements concerning the appropriateness of a drug prescription for an individual diagnosis. Such data can therefore be collected by trained personnel who are not doctors, pharmacists or nurses.

STEP 2 In-depth investigation of specific problems

Once an area of inappropriate medicine use is identified, it should be examined in depth in order to determine the size and nature of the problem and the reasons underlying the problem. Such investigation may include, for example:

- **Prescription audit** to see if the treatment of a specific disease is in accordance with guidelines (see section 6.3 on the complementary indicator – the percentage of prescribing encounters in accordance with standard treatment guidelines).
- **Qualitative methods** to determine the causes of a drug use problem (see section 6.4). There may be many rational reasons why people use medicines inappropriately; unless these reasons are understood it is impossible to devise an effective strategy to change behaviour.
- **Drug utilization review** to see if the use of a specific medicine is in accordance with previously agreed criteria (see section 6.5).

STEP 3 Develop, implement and evaluate strategies to correct the problem

Strategies to promote more rational use of medicines are described in chapter 7. Box 8.3 in section 8.2 describes how the use of injections was investigated in Indonesia and then a strategy developed and implemented to reduce inappropriate use.

6.2 Analysis of aggregate medicine use data

Aggregate data can be used to conduct ABC analysis, therapeutic category analysis, VEN analysis, and to enable the use of defined daily dose in analyses (MSH 1997, chapter 41, pp. 633–642). All these methods are very powerful tools that a DTC can and should use to manage the formulary medicines list and identify medicine use problems. Aggregate data on drug use can be obtained from many sources within the health-care system, including procurement records, warehouse drug records, pharmacy stock and dispensing records, medication error records and adverse drug reaction (ADR) records. Aggregate data sources can be used to obtain a variety of information, for example:

- Cost of drugs used – individual drugs and drug categories (see section 6.2.1)
  - — Which are the most expensive drugs?
  - — On which drugs is most money spent?
  - — What are the most expensive therapeutic categories?
  - — What is the percentage of the budget spent on certain drugs or drug classes?
- Quantities (in units, for example tablets) of drugs used (see section 6.2.4)
  - — Which are the most frequently and infrequently used drugs?
  - — Does actual drug consumption match expected consumption according to morbidity records?

— Per capita use of specific products

- Relative use of therapeutically substitutable products (see section7.3 on generic substitution and therapeutic interchange)
- Incidence of adverse drug reactions (see section 5.4.2) and medication errors (see section 5.2).

All of this data may be broken down (disaggregated) by area of the hospital – surgical wards, medical wards, casualty department, etc. Any identified problems discovered in reviewing this data should be promptly analysed by the DTC, and a strategy to remedy the problem instituted.

6.2.1 ABC analysis

Most pharmacists and managers know that only a few drug items account for the greatest drug expenditure. Often 70–80% of the budget is spent on 10–20% of the medicines. ABC analysis is the analysis of annual medicine consumption and cost in order to determine which items account for the greatest proportion of the budget. ABC analysis can:

- Reveal high usage items for which there are lower-cost alternatives on the list or available in the market. This information can be used to:
  - — choose more cost-effective alternative medicines
  - — identify opportunities for therapeutic substitution
  - — negotiate lower prices with suppliers.
- Measure the degree to which actual drug consumption reflects public health needs and so identify irrational drug use, through comparing drug consumption to morbidity patterns.
- Identify purchases for items not on the hospital essential medicines list i.e. the use of non-formulary medicines.

ABC analysis can be applied to drug consumption data over a one-year period or shorter. It can also be applied to a particular tender or set of tenders. A summary of the steps is shown in box 6.1.

After an ABC analysis has been completed, individual drugs, particularly from category A, should be examined to identify duplication, use of non-formulary drugs and expensive drugs for which there are cheaper therapeutic equivalents. In some cases the ABC analysis may need to take into account varying price levels, brand products and medical devices, such as syringes. ABC analysis can also be used to analyse one therapeutic class, where all the medicines have equal or similar efficacy. In summary, the major advantage of ABC analysis is that it identifies those medicines on which most of the budget is spent; a major disadvantage is that it cannot provide information to compare medicines of differing efficacy.

Using a spreadsheet computer programme such as Microsoft Excel or Lotus 1-2-3 makes ABC analysis much easier.

The ABC analysis shown in table 6.1 identifies five drug/chemical entities as consuming 62% of the budget: benzyl penicillin 1 MU injection, chloroxylenol 5% solution, fortified procaine benzyl penicillin 4 MU injection, ampicillin 125 mg/5 mL powder for suspension and 100 mL chlorhexidine 5% solution. The next step would be to investigate whether these high-cost items were all needed and were being used effectively. Such investigation might involve a drug utilization review (section 6.5) for the different antibiotics or a comparison of the efficacy and price for the different antiseptics.

BOX 6.1 SUMMARY OF STEPS OF ABC ANALYSIS

- List all the items consumed or purchased.
- For each item consumed or purchased, write down
  - — the unit cost of each item (using the prices for a fixed date if prices have varied over time)
  - — the quantity of each item consumed or purchased.
- Calculate the monetary value of consumption by multiplying the unit cost by the number of units consumed for each item. The total value of consumption is the sum of all items.
- Calculate the percentage of the total consumption value represented by each item by dividing the value of each item by the total consumption value.
- Rearrange the list by ranking the items, in descending order, by percentage value of total consumption.
- Calculate the cumulative percentage value of the total value for each item; beginning with the first (top) item, add its percentage to that of the item below it in the list.
- Categorize your items into:
  - — A, those few items accounting for 75–80% of total value
  - — B, those items which take up the next 15–20%
  - — C, the bulk of items which only account for the remaining 5–10% of value.

Typically, class A items constitute 10–20% of all items, with class B items constituting another 10–20% and the remaining 60–80% being in category C.

The results may be presented graphically by plotting the percentage of total cumulative value on the vertical or y axis and the number of items (accounting for this cumulative value) on the horizontal or x axis.

6.2.2 Therapeutic category analysis

Building on the ABC analysis, therapeutic category analysis can:

- identify therapeutic categories that account for the highest consumption and greatest expenditures
- indicate potential inappropriate use if taken together with information on the morbidity pattern
- identify medicines that are overused or whose consumption is not accounted for by the number of cases of a particular disease, for example chloroquine and malaria
- help the DTC choose the most cost-effective drugs within a therapeutic class and to choose alternative medicines for therapeutic substitution.

The procedure is similar to ABC analysis, and the steps are shown in box 6.2. As in ABC analysis, a small number of high-cost therapeutic categories account for most of the expenditure. More detailed analysis can be performed within each high-cost category to identify the higher cost drugs and more cost-effective therapeutic alternatives.

6.2.3 Vital, essential and non-essential (VEN) analysis

Sometimes there are insufficient funds to buy all the desired medicines. VEN analysis is a well-known method to help set up priorities for purchasing medicines and keeping stock. Drugs are divided, according to their health impact, into vital, essential and non-essential categories. VEN analysis allows medicines of differing efficacy and usefulness to be

Table 6.1 **ABC Analysis example – Calculations and Ranking**

PRODUCT DESCRIPTION	Basic unit	Unit price US$	Total units	Value (US$)	% Total value	Rank by value	Cumu-lative	
Benzylpenicillin 1MU inj	amp	0.5276	144,000.00	75,974.40	25.66%	1	**25.7%**	A
Chloroxylenol 5% solution	ml	0.0034	10,728,000.00	36,475.20	12.32%	2	**38.0%**	A
Fort. Procaine Penicillin 4MU inj	vial	0.3026	100,000.00	30,260.00	10.22%	3	**48.2%**	A
Ampicillin 125mg/5ml powder for susp, 100ml	bot	0.5119	43,970.00	22,508.24	7.60%	4	**55.8%**	A
Chlorhexidine 5% solution	ml	0.0073	2,504,000.00	18,279.20	6.17%	5	**62.0%**	A
Chlorhexidine+Cetrimide 1.5%+15% sol	ml	0.0064	1,552,000.00	9,932.80	3.36%	6	**65.3%**	B
Erythromycin 250mg tab	tab	0.0350	262,000.00	9,170.00	3.10%	7	**68.4%**	B
Cotrimoxazole 400mg/80mg tab	tab	0.0098	860,000.00	8,428.00	2.85%	8	**71.3%**	B
Gentamicin Sulfate 80Mg Inj, 2ml	amp	0.0628	130,800.00	8,214.24	2.77%	9	**74.1%**	B
Chloroquine 50mg base/ml syrup	ml	0.0014	5,610,000.00	7,854.00	2.65%	10	**76.7%**	B
Multivitamin tab/caps	tab	0.0022	3,395,000.00	7,469.00	2.52%	11	**79.2%**	B
Hyoscine N-Butylbromide 10mg tab	tab	0.0174	380,000.00	6,612.00	2.23%	12	**81.5%**	C
Water for injection 10ml	amp	0.0287	220,500.00	6,328.35	2.14%	13	**83.6%**	C
Dipyrone 500mg/ml inj, 5ml	amp	0.0898	65,000.00	5,837.00	1.97%	14	**85.6%**	C
Metronidazole 200mg tab	tab	0.0052	1,080,000.00	5,616.00	1.90%	15	**87.5%**	C
Pseudoephedrine 60mg/Triprolidine 2.5mg tab	tab	0.0536	100,000.00	5,360.00	1.81%	16	**89.3%**	C
Metronidazole 200mg/5ml suspension	ml	0.0055	900,000.00	4,950.00	1.67%	17	**91.0%**	C
Nitrofurantoin 100mg tab	tab	0.0055	860,000.00	4,730.00	1.60%	18	**92.6%**	C
Benzoin, Compound Tincture	ml	0.0067	532,000.00	3,564.40	1.20%	19	**93.8%**	C
Oxytocin 10 IU Inj, 1ml	amp	0.2468	14,500.00	3,578.60	1.21%	20	**95.0%**	C
Vitamin B Complex tab	tab	0.0025	1,440,000.00	3,600.00	1.22%	21	**96.2%**	C
Calcium Gluconate 600mg tab	tab	0.0032	995,000.00	3,184.00	1.08%	22	**97.3%**	C
Codeine Phosphate 15mg/5ml linctus	ml	0.0052	490,000.00	2,548.00	0.86%	23	**98.1%**	C
Ferrous Salts, equiv. to 60mg Iron base	tab	0.0007	3,280,000.00	2,296.00	0.78%	24	**98.9%**	C
Hydrogen Peroxide 6% solution	ml	0.0016	632,000.00	1,011.20	0.34%	25	**99.2%**	C
Piroxicam 20mg capsules	cap	0.0099	97,000.00	960.3	0.32%	26	**99.6%**	C
Phenobarbitone 60 mg tab	tab	0.0047	135,000.00	634.5	0.21%	27	**99.8%**	C
Prednisolone 5mg tab	tab	0.0079	65,000.00	513.5	0.17%	28	**99.9%**	C
Chlorphenamine maleate 4mg tab	tab	0.0009	555,000.00	499.5	0.17%	29	**100.1%**	C
Propranolol 40 mg tab	tab	0.0067	33,000.00	221.1	0.07%	30	**100.2%**	C
Total				**296,046.08**				

Source: *Managing Drug Supply*, 1997

BOX 6.2 THERAPEUTIC CATEGORY ANALYSIS

- Do the first three steps of ABC analysis to produce a list of all items by volume and value of consumption.
- Assign a therapeutic category to each drug using the *WHO model list of essential medicines* (WhO 2002a) or according to another reference manual such as the Pharmacologic-Therapeutic Classification system used by the American Hospital Formulary Service (AHFS) or the Anatomical Therapeutic Chemical (ATC) classification system adopted by WHO.
- Rearrange the list into therapeutic categories and sum the percentage value of items in each category, in order to identify the categories accounting for greatest expenditure.

compared, unlike ABC and therapeutic category analyses, where only drugs of similar efficacy or action can be compared.

- **vital drugs (V)**: potentially life-saving or crucial to providing basic health services
- **essential drugs (E)**: effective against less severe but significant forms of disease, but not absolutely vital to providing basic health care
- **non-essential drugs (N)**: used for minor or self-limited illnesses; these may or may not be formulary items and efficacious, but they are the least important items stocked.

Many people find it relatively easy to classify medicines as 'N' but very difficult to distinguish between the 'V' and 'E' categories; they prefer to classify medicines as either essential or non-essential. This does not matter, provided that the system clearly defines the different categories used and these categories allow for clear prioritization amongst items. Box 6.3 shows the steps of VEN analysis, together with some sample guidelines for establishing VEN categories. Once a VEN analysis is done, a comparison should be made between the ABC and VEN analyses in order to identify whether there is relatively high expenditure on low-priority drugs. In particular, effort should be made to delete any 'N' drugs that are in the high cost/high consumption category A of the ABC analysis.

Table 6.2 shows a real example of a VEN analysis from Malawi, where all drugs deemed non-essential were deleted from the National Essential Drugs List.

In Malawi some medicines were regarded as non-essential because more effective alternative medicines were listed as vital or essential. For example, ferrous sulfate was regarded as non-essential, whereas ferrous sulfate with folic acid was regarded as vital. Similarly, lignocaine with adrenaline was regarded as non-essential whereas lignocaine local anaesthetic alone was regarded as essential. Some drugs were regarded as non-efficacious, for example multivitamin paediatric drops and thymol mouthwash.

6.2.4 Defined daily dose (DDD)

Drug consumption in terms of cost, as used in ABC analysis, can help us check whether the drug budget is spent in the most effective way, and identify problem drugs to investigate further. The analysis of medicine consumption in terms of unit quantities can help to identify over- and under-use of individual medications or therapeutic groups.

The defined daily dose (DDD) methodology converts and standardizes readily available product quantity data, such as packages, tablets, injection vials, bottles, into crude estimates of clinical exposure to medicines, such as the number of daily doses. The DDD is the assumed average daily maintenance dose for the medication's main indication. It is defined globally for each medicine by the WHO Collaborating Centre for Drug Statistics in Oslo,

Table 6.2 **Example of VEN Analysis in Malawi, 1995**

VITAL		ESSENTIAL		NON-ESSENTIAL	
(1) Potentially life-saving (2) Significant withdrawal side-effects (3) Major public health importance		Effective against less severe but significant forms of illness **ALL deleted from EDL**		(1) Used for minor or self limited illnesses (2) Questionable efficacy (3) High cost for marginal therapeutic advantage	
Health centre					
Phenobarbitone tab.	30mg	Lignocaine 25ml injection	1%	Lignocaine + Adrenaline inj.	1% + 1/ 200,000
Phenoxymethyl penicillin tab.	250mg	Praziquantel	600mg	Aspirin paediatric tab.	75mg
Cotrimoxazole	480mg	Gentian violet paint 500ml	0.5%	Suramin sodium injection PFR	1gm
Nystatin pessaries	100,000 I.U.	Benzyl benzoate 100 ml.	25%	Nystatin tab.	500,000 I.U.
Pyrimethamine + sulfadioxine tab	25mg+ 500mg	Magnsesium trisilicate tab.		Amodiaquine tab.	200mg Base
Ferrous sulfate + folic acid tab	200mg+ 0.5mg	Chlorpromazine tab.	25mg	Ergotamine tab.	
Adrenaline 1 ml injection	1:1,000	Aminophylline tab.	100mg	Ferrous sulfate tab.	200mg
Oral rehydration salts powder	For 1 litre	Vitamin B Complex tab.		Propranolol tab.	10mg
Gentamicin 2 ml injection	40 mg/ml	Aluminium acetate ear drops	13%	Magenta paint	20ml
Condoms with spermicide		Zinc oxide ointment	15%	Anti-snakebite venom injection	10ml
Measles vaccine (live) 10 dose vial	5 ml	Mebendazole tab.	200mg	Ergometrine maleate tab.	500mcg
Ergometrine maleate 1 ml. inj.	500mcg/ml	Ferrous sulfate paediatric mixture	60mg/5ml	Multi-Vitamins paediatric drops	
Salbutamol sulfate	4mg	Chlorpheniramine maleate tab.	4mg.	Thymol mouthwash	
Vitamin A cap.	200,000 I.U.	Lidocaine dental cartridge + Adrenaline	2% + 1/ 80,000		
District hospital					
Diazepam 2 ml. Injection	5 mg/ml	Diazepam tab.	5mg		
Atropine sulfate 1ml. Injection	600mcg/ml	Paracetamol tab.	500mg		
Nalidixic acid tab.	500mg	Codeine phosphate tab.	15mg		
Isoniazid and Thiacetazone tab.	300mg 150mg	Amoxycillin elixir	125mg/5ml		
Digoxin tab.	250mcg	Erythromycin suspension	125mg/5ml		

Key : I.U. = International Unit; mcg = µg = microgram ; gm = g = gram
Source: Malawi Essential Drugs Programme, 1995.

BOX 6.3 SUMMARY OF STEPS OF VEN ANALYSIS

1 Each DTC member should classify all the medicines as V, E, or N

2 The results of each member's classification should be compiled and an overall classification agreed in the DTC

The DTC should then:

3 identify and limit therapeutic duplication

4 examine all the N items and where possible decrease the quantities purchased or eliminate them

5 reconsider proposed purchase quantities, buying V and E items before N items and ensuring that safety stocks are higher for V and E items

6 monitor drug ordering and stock levels for V and E items more closely than for N items.

Sample guidelines for VEN categories

Characteristics of the drug and target condition	Vital	Essential	Non-essential
Occurrence of target condition			
% of population affected	>5%	1–5%	<1%
Average number of patients treated per day in an average facility	>5	1–5	<1
Severity of target condition			
Life-threatening	Yes	Occasionally	Rarely
Disabling	Yes	Occasionally	Rarely
Therapeutic effect of drug			
Prevents serious disease	Yes	No	No
Cures serious disease	Yes	Yes	No
Treats minor, self-limited symptoms and conditions	No	Possibly	Yes
Has proven efficacy	Always	Usually	Maybe
Does not have proven efficacy	Never	Rarely	Maybe

Norway, (http://www.whocc.no; see annex 6.1 for addresses and the DDDs for some medicines). The DDD is based on the average maintenance dose for adults, but it can be adjusted for paediatric medicine use.

The units in the recommended dose of a medicine may be milligrams for solid oral formulations like tablets and capsules or millilitres for liquid oral or injection formulations. Converting aggregate quantities available from pharmacy inventory records or sales statistics into DDDs roughly indicates how many potential treatment days of a medicine have been procured, distributed or consumed. The medicines can then be compared, using units such as:

- no. of DDD per 1000 inhabitants per day, for total drug consumption
- no. of DDD per 100 beds per day (100 bed-days), for hospital use.

For instance, if the calculations for amoxicillin show that there were 4 DDDs per 1000 inhabitants per day in 2002, this suggests that on any given day, for every 1000 persons, 4 adults received a daily dose of 1 g of amoxicillin. If calculations of gentamicin use are

expressed as 2 DDD per 100 bed-days, this tells us that, for every 100 beds in the hospital, every day 2 patients received 240 mg of gentamicin. The assigned DDD for amoxicillin is 1 g and for gentamicin is 240 mg. These interpretations assume that the prescribed daily dose (the quantity actually prescribed to a patient) is the same as the defined daily dose, although this may not, in fact, be the case.

These DDD units can then be used to compare consumption of different medicines within the same therapeutic group, which may have similar efficacy but different dose requirements, or medicines that belong to different therapeutic groups. Medicine utilization can be compared over time for monitoring purposes and to measure the impact of DTC interventions to improve the use of medicines. Consumption in different geographic areas or hospitals may also be compared using this methodology. Cost per DDD can also be used to compare the cost of different medicines within the same therapeutic category where the medicines have no treatment duration, such as analgesics and antihypertensives.

Important points about DDDs

- The DDD is a technical unit of measurement, established by convention, based on review of the available information of the doses recommended by the manufacturer, published drug trials and expert recommendations, and medical practice in a selection of countries. What is actually prescribed to a patient can vary according to both the illness treated and local guidelines. In such situations, the **prescribed daily dose** (PDD) is established by reviewing a sample of prescriptions and then used to convert readily available aggregate data in the same way that the DDD is used. When what is actually prescribed differs significantly from the DDD, the reasons and implications must be understood before the findings can be interpreted correctly.
- DDDs provide a unit of measurement that is independent of price and formulation, making it possible to assess trends in consumption of medicines and to perform comparisons between population groups and health-care systems.
- DDDs have not been established for topical medicines, vaccines, general/local anesthetics, contrast media and allergen extracts.
- The DDD method should only be used in settings where reliable procurement, inventory or sales data have been recorded.

Box 6.4 shows the steps involved in calculating DDDs, together with an example.

Table 6.3 shows a detailed therapeutic category analysis of different antihypertensive medicines using DDDs and comparing:

- consumption in units (tablet/capsules)
- consumption in monetary value
- cost per DDD
- cost per course of treatment.

The data in the table show that although methyldopa has the second lowest unit price of the six oral antihypertensives, its cost per DDD and cost per monthly treatment are the highest. Assuming that monthly treatments are prescribed, the total usage quantities suggest that slightly more than half of the patients were treated with methyldopa. There is evidence establishing thiazide diuretics and beta-blockers as first-line antihypertensives, so a DTC might investigate why the usage of methyldopa is more than twice that of propranol and atenolol combined. If appropriate, a shift from using methyldopa to one of the beta-blockers would result in therapy that is consistent with the evidence base and significant cost savings.

BOX 6.4 SUMMARY OF STEPS OF DDD CALCULATION

Steps	Example
1 Find out the total amount of medicines used or procured in one year in terms of the number of units (tablets, capsules, injections) and the strength (mg, g (gm), IU)	Yearly amounts of methyldopa used by a provincial hospital and surrounding clinics, covering a population of 2 million: 25 000 tablets of methyldopa 250 mg, and 3 000 tablets of methyldopa 500 mg
2 Calculate the total quantity consumed in one year in terms of mg/g/I.U. by multiplying the number of units (tabs, caps, inj.) by the strength of dose	Total yearly consumption of methyldopa = (25 000 x 250 mg) + (3000 x 500 mg) = 7 750 000 mg (7750 g)
3 Divide the total quantity by the assigned DDD for that medicine	Methyldopa assigned DDD = 1 g Thus, no.of DDDs of methyldopa consumed = 7750 g/1 g = 7750 DDD
4 Divide the total quantity by the number of patients (if known) or by the population (as shown)	Annual consumption of methyldopa = 7750 DDD per 2 000 000 inhabitants per year = 3.875 DDD per 1000 inhabitants per year

Table 6.3 **Comparing consumption and costs of antihypertensives**

Drug name	atenolol	hydralazine	methyldopa	nifedipine	propranolol	propranolol
Strength	100mg	50mg	250mg	10mg	40mg	80mg
Basic unit	tab	tab	tab	tab	tab	tab
Basic unit price (US$)	0.0800	0.0090	0.0600	0.0675	0.0040	0.0060
Total usage in basic units	29,000	86,000	443,500	7,000	70,000	5,000
Value of annual usage (US$)	2,320	774	26,610	473	280	30
No. units per DDD	1	2	4	3	4	2
Cost per DDD (US$)	0.0800	0.0180	0.2400	0.2025	0.0160	0.0120
Standard days of treatment	30	30	30	30	30	30
Basic units per course of treatment	30	60	120	90	120	60
Annual no. courses of treatment	966.7	1,433.3	3,695.8	77.8	583.3	83.3
Cost (US$) per course of treatment	2.40	0.54	7.20	6.08	0.48	0.36

Source: *Managing Drug Supply*, 1997, chapter 41, p.641.

6.3 WHO/INRUD drug use indicators for health facilities

The WHO/INRUD drug use indicators are intended to measure aspects of health provider behaviour in primary health-care facilities in a reliable way, irrespective of who collects the data. The indicators provide information to health-care managers concerning medicine use, prescribing habits and important aspects of patient care. All the indicators have been extensively field-tested in many countries and found to be relevant, easily generated and measured, valid, consistent, reliable, representative, sensitive to change, understandable, and action oriented. DTCs can use indicator studies to:

- **describe current treatment practices** to determine whether there are problems in medicine use, and which facilities or prescribers have problems. When an indicator study shows unacceptable results, the DTC can investigate the problem in more depth and then take action to improve these results.
- **show trends over time** through the repeated measurement of the indicators so providing a monitoring mechanism. Prescribers and facilities whose performance falls below a specific standard of quality can be targeted for more intensive supervision.
- **motivate health-care providers** and DTC members to improve and follow established health-care standards.
- **evaluate the impact of interventions** designed to change prescribing behaviour by measuring indicators in control and intervention facilities before and after the intervention (see section 7.6).

In addition to showing the WHO/INRUD indicators (which are basically designed for primary health-care facilities), box 6.5 also shows a selected list of indicators for medicine use in hospitals, particularly for inpatients. These hospital indicators have not been field-tested and are not widely accepted as the WHO/INRUD ones are, and they cannot replace a drug use evaluation (section 6.5). Since most of these indicators do not relate diagnosis to disease, they cannot tell us exactly what proportion of people were treated correctly or the exact nature of the drug use problem; they can only indicate that there is a drug use problem. Furthermore, different disease patterns and prescriber type will greatly affect the indicators, so analysis should be done by diagnosis or prescriber type if these vary between the facilities to be compared.

The number of prescribing encounters per facility and the number of facilities which should be examined will depend on the objective of the study and are described in detail elsewhere (WHO 1993). If the objective of the study is to describe drug use problems in a sample of facilities that is representative of a majority, then at least 30 prescribing encounters in each of 20 facilities (a total of 600 prescribing encounters) should be examined. If fewer health facilities are examined, then more prescribing encounters should be examined. If the objective is to study prescribers in one facility, as may be the case for a hospital DTC, then at least 100 prescriptions should be obtained at the single facility or department; if there is more than one prescriber, 100 prescriptions for each individual prescriber should be obtained.

6.4 Qualitative methods to investigate causes of problems of medicine use

Quantitative methods of data collection using aggregate data, health facility indicators or drug utilization evaluation can tell us if there is a medicine use problem, the nature of the problem and its size. However, these methods do not tell us **why** there is a problem. Figure 6.1 shows some of the factors that influence drug use. Knowing why prescribers and patients act as they do, and which factors are influencing them, is essential to designing

BOX 6.5 DRUG USE INDICATORS

WHO/INRUD drug use indicators for primary health-care facilities

Prescribing indicators:

- Average number of drugs per encounter
- Percentage of drugs prescribed by generic name
- Percentage of encounters with an antibiotic prescribed
- Percentage of encounters with an injection prescribed
- Percentage of drugs prescribed from essential medicines list or formulary

Patient care indicators:

- Average consultation time
- Average dispensing time
- Percentage of drugs actually dispensed
- Percentage of drugs adequately labelled
- Patients' knowledge of correct doses

Facility indicators:

- Availability of essential medicines list or formulary to practitioners
- Availability of standard treatment guidelines
- Availability of key drugs

Complementary drug use indicators:

- Percentage of patients treated without drugs
- Average drug cost per encounter
- Percentage of drug cost spent on antibiotics
- Percentage of drug cost spent on injections
- Percentage of prescriptions in accordance with treatment guidelines
- Percentage of patients satisfied with the care they receive
- Percentage of health facilities with access to impartial drug information

Source: WHO (1993). This manual provides practical guidance on how to measure these indicators.

Selected indicators used in hospitals

Average number of days per hospital admission
% drugs prescribed that are consistent with the hospital formulary list
Average number of drugs per inpatient-day
Average number of antibiotics per inpatient-day
Average number of injections per inpatient-day
Average drug cost per inpatient-day
% surgical patients who receive appropriate surgical prophylaxis
Number of antimicrobial sensitivity tests reported per hospital admission
% of inpatients who experience morbidity as a result of a preventable ADR
% of inpatients deaths as a result of a preventable ADR
% of patients who report adequate post-operative pain control

Sources: *Zimbabwe DTC manual* (1999); Draft manual on *How to investigate antimicrobial use in hospitals*, MSH (1997), RPM, HRN-A-00-92-00059-13; *Manual of indicators for drug use in Australian hospitals*, NSW Therapeutic Assessment Group Inc.

Figure 6.1 **Some factors influencing drug use**

Source: INRUD materials from the WHO/INRUD Promoting Rational Drug Use Course.

effective interventions to change behaviour and correct the problem. Qualitative methods are used to investigate the 'why' of prescriber and patient behaviour.

Four methods to collect relevant information are briefly described and summarized in Table 6.4. Analysis generally requires the identification of common themes or patterns within the data to help explain the primary and secondary reasons underlying the incorrect use of drugs by the target groups (patients or prescribers). It should be noted here that the overall design of a qualitative study is a complex process and usually requires the input and expertise of a social scientist. A more detailed description of this type of investigation is therefore beyond the scope of this manual.

A **focus group discussion** is a group discussion lasting 1–2 hours on a certain topic, organized by the researcher. The group should consist of a small number (6–10) of homogeneous people, who share similar characteristics such as age, gender or type of work (for example, a group of prescribers or a group of mothers). A trained moderator encourages participants to reveal underlying opinions, attitudes and reasons for the problem being studied. The discussion is recorded, either on tape or by two observers, and analysed systematically to identify key themes and issues. Focus group discussions can be used by a DTC to identify a range of beliefs, opinions and motives of a target group, for example doctors, nurses, pharmacists, paramedical staff and patients.

The **in-depth interview** is an extended discussion between a respondent and a knowledgeable skilled interviewer. The discussion is flexible and often unstructured, allowing an interviewer to encourage the respondent to talk at length about a particular predefined topic of interest, which may include 10–30 related topics. The in-depth interview technique can be used to expand the results of a quantitative study by exploring the reasons underlying the behaviour of the persons responsible for drug use problems. It can also be used in evaluating the impact of an intervention to promote more rational drug use.

Table 6.4 **Summary of qualitative methods**

METHOD	ADVANTAGES	DISADVANTAGES
Focus Group Discussion • < 2-hour recorded discussion • 6–10 non-random respondents • 2–4 discussions for each significant target population • Moderator leads discussion • Respondents have similar characteristics e.g. age, gender, social status • Discussion topics pre-defined • Informal, relaxed, ambient • Reveals beliefs, opinions and motives	Inexpensive Quick Easy to organize Identifies a range of beliefs	• Groups may not represent the larger population • Successful outcome is very dependent on the skills of the moderator who must balance outspoken participants against shy ones. • Tape recorders may inhibit participants but a note-taker may miss some data
In-depth Interviews • One-to-one extended interview • Questions are pre-determined but open-ended • Often covers up to 30 topics • Reveals beliefs, attitudes, and knowledge	Can reveal unsought but significant data	• May generate lots of data which are difficult to manage • Time-consuming and expensive • Bias due to respondent saying things to please the interviewer • Different interviewers may interview differently
Structured Observation • Data collection instrument is structured • Observers are trained to blend into their surroundings • Observers are trained to record what they actually see • Useful for recording provider – patient interactions • Assesses actual behaviour	Observes actual behaviour as opposed to stated behaviour, which may not be the same	• May be time consuming and expensive • Observation may cause change in the behaviour of health workers • Different observers may observe differently
Structured Questionnaires • Questions are standardized with a fixed set of responses or options • Respondents are selected so as to represent the larger population • Useful for a large sample of respondents • Measures the frequency of attitudes, beliefs, and knowledge	Can generalize the results to the wider population	• Interviewers may ask questions and interpret answers incorrectly • Different interviewers may ask questions differently • Questions may be ambiguous • Respondents may give answers to please the interviewer

The **structured observation** study method utilizes trained people to observe a series of encounters between health providers and patients, following a structured form or checklist. The observers record behaviours and impressions they witness during the encounters. In some studies, they may record a score, based upon a set of specially prepared indicators, for each observed interaction. In general 10–20 patient–provider encounters per facility in 10 facilities (or 10–20 encounters per prescriber/dispenser in the case of a single hospital department) are observed, but the exact number would depend on the study objectives. The structured observation method can be used to study behaviours such as the interactions between staff and patients (for example the quality of communication) or the giving of injections. The data can be used independently or as a supplement to other study methods.

Using a **structured questionnaire** involves the preparation of a list of questions with a fixed set of responses or options in order to collect the desired information in a standard way from all respondents. The questionnaires may be administered by an interviewer or completed alone by respondents. Questions can focus on factual material, such as what a respondent knows about standardized diarrhoea treatment. Alternatively, questions can focus on a respondent's attitudes, opinions and beliefs about the subject matter. Ideally the respondents are chosen randomly and the number will depend on the objectives of the study. The questionnaire method can be used by a DTC to quantify the frequency of attitudes, beliefs and knowledge about medicine use.

6.5 Drug use evaluation (drug utilization review)

Drug use studies using aggregate data or health facility indicators may indicate that there is over- or under-consumption of medicines, and qualitative studies may indicate why certain health staff and patients behave the way they do. However, such studies do not provide detail about the exact nature of the irrational use. Such details may concern incorrect medicine choices, incorrect dose, prescribing drugs that cause ADRs or drug interactions, and the use of expensive drugs when cheaper ones would do.

Drug use evaluation (DUE) is a system of ongoing, systematic, criteria-based evaluation of drug use that will help ensure that medicines are used appropriately (at the individual patient level). If therapy is deemed to be inappropriate, interventions with providers or patients will be necessary to optimize drug therapy. A DUE is drug- or disease-specific and can be structured so that it will assess the actual process of prescribing, dispensing or administering a drug (indications, dose, drug interactions, etc.). DUE is the same as **drug utilization review** (DUR) and terms are used synonymously.

Medication use evaluation (MUE) is similar to DUE but emphasizes improving patient outcomes and individual quality of life; it is, therefore, highly dependent on a multidisciplinary approach involving all professionals dealing with drug therapy. An MUE will assess clinical outcomes (cured infections, decreased lipid levels, etc.).

The goal of a DUE or MUE is **to promote optimal medication therapy** and ensure that drug therapy meets current standards of care. Additional objectives may include:

- creating guidelines (criteria) for appropriate drug utilization
- evaluating the effectiveness of medication therapy
- enhancing responsibility/accountability in the medicine use process
- controlling medicine cost
- preventing medication related problems, for example adverse drug reactions, treatment failures, over-use, under-use, incorrect doses and non-formulary medicine use

- identifying areas in which further information and education may be needed by health-care providers.

Once the main problem areas have been identified, (from aggregate data, health facility indicators, qualitative studies, other DUE studies, or even recommendations from DTC members), a DUE system can be established relatively quickly.

6.5.1 The steps of a DUE

The steps of a DUE are as follows. An example is shown in box 6.7.

STEP 1 Establish responsibility

It is the responsibility of the DTC to establish procedures for the implementation of a DUE programme; this includes appointing a responsible member of the DTC or a subcommittee to monitor and supervise the DUE process in the hospital or clinics. Ideally the DTC should establish annual plans, outlining which medicines or clinical conditions will be a part of the DUE process.

STEP 2 Develop the scope of activities and define the objectives

The DTC should decide upon the objectives of the DUE and the scope of the activities necessary. The scope can be very extensive or it can focus on a single aspect of drug therapy and will depend upon the type of problem identified, for example:

- overuse of a more expensive medicine when a cheaper equivalent is available, as revealed in aggregate data
- incorrect use (indication, dosage, administration) of a particular drug, as revealed in patient charts, medication error reports, ADR reports
- inappropriate choices of antibiotic, as revealed in antibiotic sensitivity reports
- a poor dispensing process, as revealed by patient complaints or feedback.

Due to the large number of medicines available at a hospital or clinic, the DTC must concentrate on those medicines with the highest potential for problems in order to get the most return on the work involved. These high-priority areas include:

- high-volume drugs
- expensive drugs
- drugs with a narrow therapeutic index
- drugs with a high incidence of ADRs
- critically important therapeutic categories, for example cardiovascular, emergency, toxicology, intravenous drugs, chemotherapy and narcotic analgesics
- antimicrobial drugs, prophylactic and therapeutic
- drugs undergoing evaluation for addition to the formulary
- drugs used for non-labelled indications
- drugs used in high-risk patients
- common clinical conditions often poorly treated.

STEP 3 Establish criteria for review of the medicine

Establishing DUE criteria is extremely important, and is the responsibility of the DTC. DUE criteria are statements that define correct drug usage with regard to various components, as shown in box 6.6. Criteria for the use of any medicine should be established using the hospital's STGs (assuming that they have been correctly developed). In the absence of hospital STGs, criteria may be based on recommendations from national or other locally available satisfactory drug use protocols, other relevant literature sources, and/or recognized international and local experts. Credibility, and staff acceptance, of the DUE relies on using criteria that have been developed from reading established evidence-based medicine information from reputable sources and that have been discussed with prescribers.

BOX 6.6 COMPONENTS OF DRUG USE FOR DUE CRITERIA

- **uses:** appropriate indication for drug, absence of contraindications
- **selection:** appropriate drug for clinical condition
- **dosing:** indication-specific dosing, intervals and duration of treatment
- **interactions:** absence of interactions – drug–drug, drug–food, drug–laboratory
- **preparation:** steps involved with preparing a drug for administration
- **administration:** steps involved in administration, quantity dispensed
- **patient education:** drug and disease-specific instructions given to patients
- **monitoring:** clinical and laboratory
- **outcome, for example:** decreased blood pressure, blood glucose, asthma attacks

Reviewing many criteria will make the DUE process more difficult, and may impair successful completion of the review. Therefore the number of criteria established for each medicine is often between 3 and 5. Once the criteria are established, thresholds or benchmarks are decided for each criterion in order to define the expectations or goals for compliance with the criteria. Ideally one would like 100% of all cases to comply with the criteria, but in reality this may not be possible, and a DTC might decide to set a threshold of 90–95% compliance below which they would instigate corrective action.

STEP 4 Data collection

Data may be collected **retrospectively**, from patient charts and other records, or **prospectively**, at the time a medicine is prepared or dispensed. Retrospective data collection may be quicker and is best accomplished away from the patient care areas and distractions. The advantage of a prospective review is that the reviewer can intervene at the time the medicine is dispensed to prevent errors in dosage, indications, interactions or other mistakes. A particular example of this is the computerized systems used in some pharmacies; here the computer warns the pharmacist if patient data being entered into the computer fails to meet established criteria and requires them to correct the problem(s) noted. Such a system can also provide a large database for use retrospectively.

Data must be collected from a suitable random sample of charts or prescription records from the health-care facility, usually selected by pharmacy personnel, but also by nurses or medical records personnel. The treatment of at least 30 patients, or 100 patients for common clinical conditions, should be reviewed per health facility or hospital. The larger the facility and the more practitioners, the larger the number of records needed for review

and analysis. Data collection forms based on the criteria can be configured into simple 'yes/no' questions or may involve the filling in of open questions (see annex 6.2). Sources of data include patient charts, dispensing records, medication administration records, laboratory reports, ADR reports, medication error reports, antimicrobial sensitivity reports, and documented staff and patient complaints.

STEP 5 Data analysis

Data are tabulated in a form that corresponds to the criteria chosen for the DUE. The percentages of cases that meet the threshold for each criteria should be calculated and summarized for presentation to the DTC. A report of all DUE programmes that are being conducted should be prepared on a quarterly basis.

STEP 6 Feedback to the prescribers and making a plan of action

After information is presented (for example on inappropriate drug use or unacceptable patient outcome), the DTC should develop conclusions about the differences between actual and desired results. In other words, how do the actual results vary from the desired benchmark or threshold levels? The DTC should then decide what follow-up action is necessary and whether to continue, discontinue or expand the functions of the DUE in question. Recommendations should include specific steps to correct any drug use problem that is evident from performing the DUE. For example, if a specific medicine is being prescribed at too high a dose, the recommendations need to specify in detail how the dosing of this medicine can be improved. Interventions to improve drug use would include feedback to the prescribers and may also include:

- education, for example letters, in-service education, workshops, newsletters, face-to-face discussions
- institution of drug order forms
- institution of prescribing restrictions
- changing the formulary list and/or manual
- changing the standard treatment guidelines
- using another DUE or continuing the present one.

STEP 7 Follow-up

In every DUE, follow-up is critical to ensure appropriate resolution of any problems. Did an intervention achieve its objective? If an intervention is not evaluated, or drug use problems are not resolved, then the DUE will have been of no use. As a part of a follow-up plan the DTC must assess the need to continue, modify or discontinue the DUE. Thus, DUE activities should be evaluated regularly (at least annually) and those that do not have a significant impact on drug use should be redesigned in order to provide measurable improvements. Common problems associated with DUEs include unclear responsibilities for different activities, poor prioritization of problems, lack of documentation, lack of personnel and inadequate follow-up. If follow-up is adequate, prescribers are likely to improve their performance in all areas knowing that they may be reviewed in the future!

BOX 6.7 DRUG USE EVALUATION AT A US HOSPITAL

In 1993 the quality assurance coordinator reported to the DTC that the rate of postoperative infections for abdominal surgery was considerably higher than the national average. The pharmacy director reported that ceftriaxone, a costly and inappropriate drug, was used for these patients. He advised that current formulary drugs, either cefoxitin or cefotetan, would be more appropriate. The DTC decided to undertake a DUE for prophylaxis of abdominal surgery wound infection. The chief surgeon was a member of the DTC and he agreed with their decision to conduct a DUE using criteria developed from recently published recommendations in the Medical Letter.

- Data collection period: January–December 1994
- Total number of cases: 162
- Date of report: January 1995
- Number of cases reviewed: 120 (74%)

Criteria	Benchmark (%)	Compliance per quarter (%)			
		1st	2nd	3rd	4th
1 Correct antibiotic selection	100	70	85	94	100
2 Correct dose	95	65	90	94	97
3 Dose: 0–2 hours preoperative	95	30	52	89	94
4 Postoperative dose: for dirty surgery only	98	78	89	82	91
5 No postoperative infection	96	90	93	96	100
6 No ADRs to drugs	97	97	100	87	97

Conclusions after the first quarter

- Criterion 1: non-first choice antibiotics (e.g.ceftriaxone) for the indicated procedure were being used instead of recommended ones (e.g. cefoxitin or cefotetan)
- Criterion 2: unnecessarily high doses of antibiotics were being prescribed
- Criterion 3: preoperative doses were being delayed because the current pharmacy procedure was to send antibiotics to the operating room rather than the preoperative area
- Criterion 4: patients not meeting the criteria for dirty surgery were also receiving antibiotics
- Criterion 5: relatively high postoperative infection rate may be reduced with increased compliance with criteria

Recommendations

- Send letter to all surgeons with information about (1) current postoperative infection rates versus the national average, (2) criteria and recommendations from the Medical Letter, (3) results of the DUE data collection, (4) estimated cost impact of inappropriate drug selection and unnecessary drug use
- Remove cefoxitin from the formulary because of its disadvantages (cost and short half-life) compared with cefotetan
- Change procedures to administer preoperative doses in the preoperative area rather than the operating room, and instruct nursing and pharmacy staff accordingly
- Add approved antibiotics to the floor stock in the preoperative area for emergencies

Continued

BOX 6.7 *CONTINUED*

Actions

- Chief surgeon informed the surgical committee about the DUE and the criteria in 1994
- A letter was sent to all surgeons in April 1994 detailing the rationale for using cefotetan, not ceftriaxone, for prophylaxis of abdominal wound surgery
- Cefoxitin was removed from the formulary: ceftriaxone could not be removed due to its use for other indications
- New procedures for administration were adopted in June and staff training started in July 1994
- Antibiotics were added to preoperative floor stock in July 1994

Follow-up

- Criterion 1: Benchmark met in 4th quarter – education of surgeons led to an improvement in selection
- Criterion 2: Benchmark met in 4th quarter – education of surgeons led to an improvement in dosing
- Criterion 3: Benchmark was not met in 4th quarter despite all the activities and was considered unrealistically high because of many factors in emergency procedures; it was therefore reduced to 93%
- Criterion 4: Education decreased unnecessary postoperative antibiotics for a short time; then surgeons began to return to old practices. The DTC sent individual letters to specific surgeons and the practice improved but still did not reach the benchmark. Cases of non-compliance were to be reported to the DTC for peer review and recommendations
- Criterion 5: Benchmark met in third quarter
- Criterion 6: Allergic reactions increased in the third quarter because of the change in floor stock procedures and the preoperative nurse failing to screen for patient allergies (previously the pharmacy screened for allergies before dispensing). Nurses then received in-service training and allergic reactions decreased, meeting the benchmark in the 4th quarter.

Source: C. Olsen, MSH

ANNEX 6.1

Defined daily doses (DDD) of some common medicines

Drug name	DDD
Preoperative medication	
atropine sulfate	1.5 mg
diazepam (inj, oral, rect)	10 mg
morphine sulfate	0.1 g
promethazine hcl	25 mg
Analgesics and NSAIDs	
acetylsalicylic acid	3 g
diclofenac sodium	0.1 g
ibuprofen	1.2 g
indomethacin	0.1 g
naproxen	0.5 g
paracetamol	3 g
pheylbutazone	0.3 g
Opioids	
codeine	0.1 g
morphine sulfate	0.1 g
pentazocine	0.2 g
pethidine	0.4 g
tramadol	0.3 g
Gout	
allopurinol	0.4 g
colchicine	1 mg
probenecid	1 g
Rheumatoid disease	
azathioprine	0.15 g
chloroquine	0.5 g
Antiallergics	
astemizole	10 mg
chlorpheniramine	12 mg
dexamethasone	1.5 mg
diphenhydramine	0.3 g
epinephrine	0.5 mg
hydrocortisone	30 mg
prednisolone	10 mg

Drug name	DDD
Anticonvulsants	
carbamazepine	1 g
diazepam	10 mg
ethosuximide	1.25 g
magnesium sulfate	3 g
phenobarbital	0.1 g
phenytoin	0.3 g
valproic acid	1.5 g
clonazepam	8 mg
Anthelmintics	
albendazole	0.4 g
levamisole	0.15 g
mebendazole	0.2 g
niclosamide	2 g
piperazine	3.5 g
praziquantel	3 g
pyrantel	0.75 g
thiabendazole	3 g
Antianginal drugs	
atenolol	75 mg
glyceryl trinitrate	5 mg
isosorbide dinitrate	60 mg
nifedipine	30 mg
Antiarrhythmics	
isoprenaline inj	90 mg
lidocaine	3 g
procainamide	3 g
propranolol	0.16 g
quinidine sulfate	1.2 g
verapamil	0.24 g
Antihypertensives	
atenolol	75 mg
captropril	50 mg
enalapril	10 mg
hydralazine	0.1 g
hydrochlorothiazide	50 mg

Drug name	DDD
methyldopa	1 g
nifedipine	30 mg
nitroprusside, sodium	50 mg
prazocin	5 mg
reserpine	0.5 mg
Heart failure drugs	
digoxin	0.25 mg
dopamine	0.5 g
epinephrine	0.5 mg
Diuretics	
amiloride	10 mg
bendrofluazide	2.5 mg
frusemide	40 mg
hydrochlorothiazide	50 mg
spironolactone	75 mg
Antithrombotics	
streptokinase	1.5 MU
Anticoagulants	
desmopressin (inj)	4.0 mcg
desmopressin (oral)	0.4 mg
desmopressin (nasal)	25 mcg
heparin	10 TU
vitamin K–phytomenadione	20 mg
warfarin sodium	7.5 mg
Anti-infectives	
albendazole	0.4 g
diethylcarbamazine	0.4 g
ivermectin	12 mg
Antischistosomals	
oxamniquine	1 g
praziquantel	3 g
Beta-lactams	
amoxycillin	1 g
ampicillin	2 g
ceftazidime	6 g
cetriaxone	2 g

Drug name	DDD
cephazolin	3 g
cefotaxime	4 g
cefuroxime	2 g
cephalexin	2 g
cephazolin	3 g
cloxacillin sodium	2 g
methicillin	4 g
imipenem	2 g
pencillin G sodium	3.6 g
pencillin V	2 g
Other antibacterials	
chloramphenicol	3 g
ciprofloxacin	1 g
clindamycin	1.2 g
doxycycline	0.1 g
erythromycin	1 g
gentamicin sulfate	0.24 g
kanamycin sulfate	1 g
metronidazole (inj/oral)	1.5 g
metronidazole pessary	0.5 g
nalidixic acid	4 g
nitrofurantoin	0.2 g
norfloxacin	0.8 g
oxytetracycline	1 g
spectinomycin	3 g
sulfadiazine	0.6 g
sulfadimidine	4 g
tetracycline	1 g
trimethoprim	0.4 g
vancomycin	2 g
Antileprosy drugs	
clofazimine	0.1 g
dapsone	0.05 g
rifampicin	0.6 g
Antituberculosis drugs	
ethambutol	1.2 g
isoniazid	0.3 g
pyrazinamide	1.5 g
rifampicin	0.6 g

Drug name	DDD
streptomycin sulfate	1 g
Antacids/peptic ulcer	
magnesium hydroxide	3 g
cimetidine	0.8 g
famotidine	40 mg
ranitidine	0.3 g
omeprazole	20 mg
Antiemetics	
metoclopramide	30 mg
promethazine	25 mg
Antispasmodics	
atropine sulfate	1.5 mg
propantheline bromide	60 mg
Laxatives	
bisacodyl (suppos./oral)	10 mg
liquid paraffin	15 g
Antidiarrhoeals	
codeine	0.1 g
loperamide	10 mg
sulfaguanidine	4 g
Hormones/contraceptive	
clomiphene	9 mg
ethinyl oestradiol	25 mcg
norethisterone	5 mg
medroxyprogesteron oral	5 mg
Insulins/antidiabetics	
chlorpropamide	0.375 g
glibenclamide	10 mg
insulins – all types	40 IU
metformin	2 g
tolbutamide	1.5 g
Thyroid/antithyroid	
carbimazole	15 mg
levothyroxine	0.15 mg
propylthiouracil	0.1 g
Miotics/antiglaucoma	
acetazolamide oral	0.75 g
pilocarpine drops–2% 4%	0.4 mL
timolol mal.– 0.25% 0.5%	0.2 mL

Drug name	DDD
Antitussives	
dextromethorphan	90 mg
diphenhydramine	0.3 g
noscapine	0.125 g
Antifungals	
amphotericin B	35 mg
clotrimazole (pessary)	0.1 g
fluconazole	0.2 g
flucytosine	10 g
griseofulvin	0.5 g
ketoconazole	0.2 g
nystatin (oral)	1.5 MU
nystatin (pessary)	0.1 MU
Antiretrovirals	
aclyclovir	4 g
zidovudine	0.6 g
Antiprotozoals	
diloxanide furoate	1.5 g
metronidazole (oral/inj)	1.5 g
tinidazole	1.5 g
Antileishmaniasis	
meglumine antimonate	0.85 g
pentamidine	0.28 g
sodium stibogluconate	0.85 g
Antimalarials	
chloroquine phosphate	0.5 g
doxycycline	0.1 g
mefloquine	1 g
primaquine phosphate	15 mg
proguanil	0.2 g
pyrimethamine	75 mg
quinine dihydrochloride	0.3 g
quinine sulfate	0.3 g
sulfadoxine/pyrimeth.	75 mg
African trypanosomiasis	
metronidazole oral	1.5 g
melarsoprol	60 mg
suramin sodium	0.27 g

Drug name	DDD
American trypanosomiasis	
benznidazole	0.4 g
nifurtimox	0.7 g
Immunosuppressives	
azathioprine	0.15 g
Antihormones	
tamoxifen	20 mg
Adrenal hormones	
dexamethasone (oral/inj)	1.5 mg
hydrocortisone (inj)	30 mg
prednisolone (oral/inj)	10 mg
Antiparkinsonism	
biperidin	10 mg
levodopa + carbidopa	0.6 g
Antianaemia	
ferrous salt (iron = 60 mg)	0.2 g
folic acid	0.3 mg
hydroxycobalamin	0.02 mg
Oxytoxics/antioxytoxic	
ergometrine maleate	0.2 mg
ergotamine tartrate	4 mg
oxtocin (inj)	15 IU
Psychotherapeutics	
amitriptyline	75 mg
chlorpromazine (inj)	0.1 g
chlorpromazine (oral)	0.3 g
clomipramine	0.1 g
diazepam (oral)	10 mg
fluphenazine (inj)	1 mg
haloperidol (inj)	3.3 mg
haloperidol (oral)	8 mg
imipramine	0.1 g
lithium carbonate (oral)	24mmol
lorazepam	2.5 mg
nitrazepam	5 mg
thioridazine	0.3 g
trifluoperazine oral	20 mg
Antiasthmatics	
aminophylline inj/oral	0.6 g
beclomethasone inhaler	0.8 mg
cromoglycic acid inhaler	40 mg
ephedrine	50 mg
epinephrine (inj)	0.5 mg
ipatropium inhaler	0.12 mg
salbutamol (inj/oral)	12 mg
salbutamol inhaler	0.8 mg
salbutamol respsol	10 mg
theophylline	0.4 g
Vitamins/minerals	
ascorbic acid (vit.C)	0.2 g
calcium gluconate	3 g
calcium lactate	2 g
nicotinamide/niacin (vitamin B3)	0.15 g
potassium chloride	3 g
pyridoxine (vitamin b6)	0.16 g
thiamine (vitamin B1)	50 MG
retinol (vitamin A)	5000 IU
Muscle relaxants	
neostigmine (inj)	60 mg
pyridostigmine (inj)	10 mg

The drugs listed here are a selection of medicines taken from WHO's *Model list of essential medicines* (WHO 2002a) and MSH's annual *International drug price indicator guide*, presented according to therapeutic category. The information presented here was correct at the time of going to press, but may have changed since. This list is not exhaustive, nor is it intended to be, in any way, a recommendation for inclusion in national or hospital formulary lists. The DDD for different drugs can be obtained from:

WHO Collaborating Centre for Drug Statistics Methodology, Postboks 100 Veitvet, Oslo, Norway (http://www.whocc.no) Tel. +47 22 16 98 11; Fax: +47 22 16 98 18; email: whocc@nmd.no

Management Sciences for Health (MSH), *International drug price indicator guide*, annual publication by MSH in collaboration with WHO, 165 Allandale Road, Boston, MA 02130-3400, USA (http://www.msh.org/publications and http://erc.msh.org). Tel. +1 617 524 7799; Fax: +1 617 524 2825; email: bookstore@msh.org

ANNEX 6.2

DUE criteria on data collection form for amikacin

This sample form has columns for four patients, but in reality there would be many more.

Patient number		**1**	**2**	**3**	**4**	
Data collector's initials						
Patient chart number						
Diagnosis						
Age						
Sex						
Weight						
Date treated						
Criteria (indicators)						
Justification for prescription 1 Serious infections caused by susceptible strains of aerobic gram-negative bacteria resistant to gentamicin and tobramycin 2 Suspected serious gram-negative infections acquired in the hospital with high resistance rates to gentamicin and tobramycin 3 In combination with an anti-pseudomonal penicillin when treating serious Pseudomonas infections	Threshold	Y/N	Y/N	Y/N	Y/N	Average
Process indicators 4 Obtain serum creatinine prior to therapy or within 24 hours of initiation of therapy 5 Loading dose of 7.5 mg/kg (IV or IM) based on ideal body weight 6 Maintenance dosage range of 15 mg/kg per day ideal weight (exception: renal compromise) 7 Therapy changed to tobramycin, gentamicin or other drug if culture/sensitivity indicates less expensive or more appropriate drug		Y/N	Y/N	Y/N	Y/N	Average
Outcome indications 8 Clinical improvement noted in patient medical records 9 Fever reduced to normal within 72 hours		Y/N	Y/N	Y/N	Y/N	Average

Y/N = yes/no

7. Promoting the rational use of medicines

Summary

Changing the use of medicines to ensure that they are used in the most effective way is the overall aim of a drug and therapeutics committee (DTC). There are three overall types of strategy to change the use of medicines:

- educational strategies that aim to inform prescribers
- managerial strategies that aim to guide the decisions of prescribers
- regulatory strategies that aim to restrict the decisions of prescribers.

A comprehensive approach with a combination of interventions (preferably of different types) is always more effective than single interventions. It is critical to assess the impact of interventions using adequate study design in order either to discontinue those that have no impact, or to gain sufficient support to continue implementation of those that do have impact.

7.1 Changing a medicine use problem

Evaluation of medicines, with a view to adding or deleting them from the formulary, is one of the most important functions of the DTC. An equally important function of the DTC is to ensure that the drugs selected for the formulary are used appropriately. If no attention is paid to how medicines are used by providers and consumers, then inappropriate use will undermine any advantages achieved by appropriate selection.

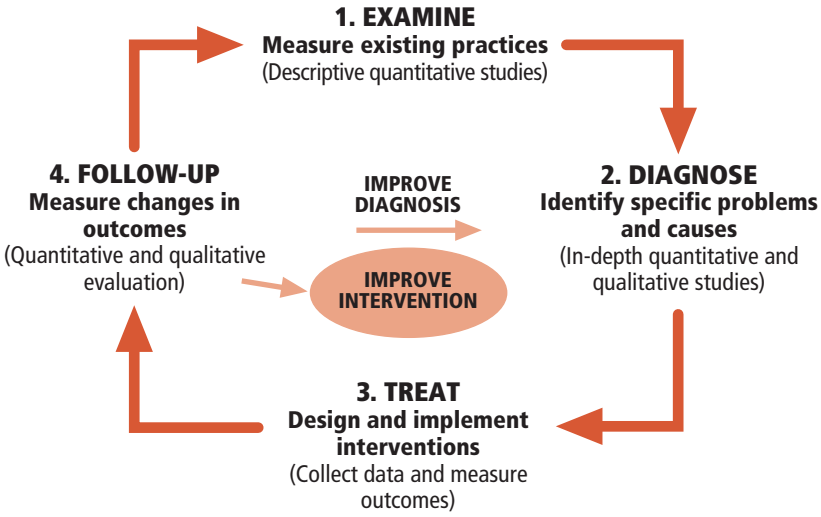
Rational use of medicines requires that the patients receive drugs appropriate to their clinical needs in doses that meet their individual requirements (right dose, right intervals and right duration). Thus, rational use includes correct prescribing, dispensing and patient adherence. In many developing countries, prescribers are not always doctors, nor dispensers pharmacists. Nurses, paramedical workers and even lay people may be involved in these processes. Promoting rational use of medicines requires that the behaviour of all persons involved in each process (prescribing, dispensing and patient use) be addressed.

Figure 7.1 summarizes the process of changing a medicine use problem.

Strategies or interventions that can be used to promote more rational drug use may be categorized into three main types:

- **educational strategies** (section 7.2), which aim to inform and persuade users
- **managerial strategies** (section 7.3), which aim to structure and guide decisions made by users
- **regulatory strategies** (section 7.4), which aim to restrict or limit the decisions of users.

Figure 7.1 **Changing a drug use problem: an overview of the process**



Source: INRUD materials from the WHO/INRUD Promoting Rational Drug Use Course.

How to choose which intervention(s) is described in section 7.5 and how to evaluate the impact of an intervention is discussed in section 7.6. However, a comprehensive approach, involving several interventions rather than just one, and the participation of staff in developing and implementing interventions, is more likely to be effective.

7.2 Educational strategies

The DTC is responsible for educational programmes for the health-care professionals within the hospital or facilities that it oversees. If these programmes are not put in place, there will be a persistent and noticeable decline in the knowledge levels of health professionals and a related decrease in rational medicine use. All professionals, particularly those involved in health care, need constant updating of their skills and knowledge. It is impossible for physicians, pharmacists, nurses, paramedical staff and others to keep up with the constant changes in the drug literature without intensive individual effort and continuing education provided by the health-care system. Educational strategies rely on the availability of standard treatment guidelines or protocols in order to set the standards of care to which prescribers should adhere.

7.2.1 In-service education programmes, workshops, seminars

The information on medicines and drug therapy is constantly changing. The DTC is responsible for ensuring that all staff receive up-to-date information, in-service education and other educational programmes. In addition, educational programmes can be used to address medicine use problems that have been identified by the DTC. The success of such programmes in terms of impact on medicine use will depend on the information presented, how it is presented, and by whom. A problem-based approach as described in the *Guide to good prescribing: a practical manual* (WHO 1994a) has been found to be particularly effective for educating prescribers at both undergraduate and postgraduate levels.

Large group meetings (more than 15 participants) can be effective if they are well prepared, targeted, use interactive methods and provide a few clear messages as to what behaviour change is expected. For example, a lecture on antimicrobial resistance in which staff sit in rows of chairs and listen to a lecturer talk about bacteriostatic or bactericidal

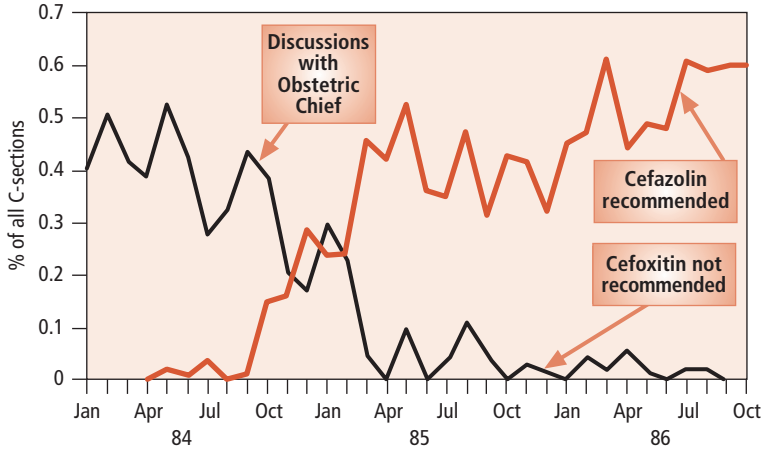
medicines for an hour is likely to have minimal effect. A more successful approach might be for the facilitator to introduce the topic of antimicrobial resistance in terms of an actual patient (or a made-up patient case) and use a problem-based approach to decide what treatment should be given. At the end it is important to summarize the discussions and leave participants with clear messages as to what should be done. Visual aids can help the discussion, but should be carefully prepared since people learn in different ways.

Small group meetings (less than 15 participants) are usually more effective than larger ones and have the advantage that they can be held at the work site for shorter periods of time and can allow more interaction and reinforcement of messages. Wherever possible, the teaching should be problem-based, using real-life examples suggested by the staff. Previously prepared material can be used to illustrate points in the subsequent discussion and/or in the summing up of the discussion. In hospitals it may be possible to group staff for an hour over tea either in the morning or afternoon on a regular basis, for example weekly, to discuss particular drug issues.

Individual teaching can be the most effective, but is also the most time-consuming. Drug representatives are the best at doing this. In 15 minutes a drug representative can persuade a doctor to change his or her prescribing practice. They do this by being charming (good communication skills), having only one or two key messages to convey, and providing visually attractive memory aids (colourful pamphlets or notepads, desk calendars, engraved pens, etc). They also use the names of opinion leaders to support claims, and always follow up a visit with a reinforcement visit. It is perfectly possible for pharmacists or members of the DTC to use the same approach, which is called **academic detailing** (O'Brien et al. 2000, Ilett et al. 2000).

Influencing opinion leaders has been shown to influence prescribing habits significantly. Health-care opinion leaders are the people that junior staff go to for advice. It may be the professor or the senior consultant, but often it is not. It may be a middle-grade doctor in a large hospital or it may be an experienced nurse in outpatients, an effective pharmacist or a 'smart' junior doctor. Identifying the opinion leaders is important and relatively easy. Once the opinion leaders have been identified, it may be a good idea to invite them to join the DTC and to target individual teaching at them. They should be provided with education, guidance and policies. These leaders are likely to be in a position to teach or direct other health-care staff on the appropriate standards of care. Figure 7.2 shows the

Figure 7.2 **Effects of opinion leader on antibiotic use.** In a US hospital, researchers approached the head of obstetrics to seek permission to replace cefoxitin with cefazolin for prophylaxis in patients undergoing caesarean section. The professor reviewed the papers and then instructed staff to make the change, with dramatic and sustained results (Everitt et al. 1990).



impact that influencing an opinion leader had on antimicrobial surgical prophylaxis in a hospital in the USA.

Educational outreach is based on small group or individual face-to-face meetings in the prescribers' workplace. As described above, it has been fully and successfully exploited by the world's pharmaceutical industry. Pharmaceutical companies employ thousands of representatives to meet face-to face-with prescribers to provide information and market their drugs. DTCs should provide educational outreach programmes of their own using locally available opinion leaders and trained educators. Principles of this type of education include:

- focusing on specific problems and targeting the prescribers
- addressing the underlying causes of prescribing problems, such as inadequate knowledge
- allowing an interactive discussion that involves the targeted audience
- using concise and authoritative materials to augment presentations
- giving sufficient attention to solving practical problems encountered by prescribers in real settings.

Patient education influences drug prescribing. Provision of regular patient education by health staff will educate patients about appropriate therapy and adherence to drug regimens, so leading to improved health outcomes. An educated patient population will have less demand for inappropriate medicines, especially antibiotics. The importance of patient education cannot be overemphasized. The more education patients receive, the more likely they are to benefit from improved health-care outcomes. Doctors, nurses, pharmacists and paramedical staff should all contribute to this effort on a routine basis.

7.2.2 Drug information resource centre/unit

Neither training nor other educational activities of the DTC can be successful and sustainable without a reliable source of unbiased information. There should be, at least, a small drug information resource centre or a library with at least two or three current authoritative reference books, and, if possible, peer-reviewed journals. Copies of the DTC's own formulary list, formulary manual and standard treatment guidelines (STGs) should be readily available (i.e. every prescriber should have a personal copy, or there should be a copy in every ward, every consulting room in outpatients and in the pharmacy). Other practical materials such as STGs for other diseases, formulary manuals and the national EML can be secured from other institutions and organizations. Drug information units may produce local bulletins that can give updated and practical drug prescribing information. Many materials can be acquired free of charge, but the DTC should request a small budget from the hospital management to cover the purchase of books, journals and bulletins.

7.2.3 Drug newsletters and bulletins

Drug newsletters can be a valuable component in providing drug information. These newsletters can be published monthly, quarterly or at longer intervals and should provide staff with unbiased and accurate information about drug therapy. Newsletters and bulletins have an advantage over formal group presentations because busy practitioners can read the information at a time that suits them. **However, printed materials, including newsletters, are unlikely to be effective in changing irrational prescribing habits unless they are combined with a more interactive teaching method**. Many drug newsletters and bulletins are already published by commercial ventures and distributed worldwide (see annex 4.1). However, a local bulletin can be an invaluable asset since it will provide more information concerning medicines and medicine-related problems of

BOX 7.1 PRINCIPLES OF EFFECTIVE DRUG NEWSLETTERS

- The reasons for prescribing behaviour are understood and are addressed, for example lack of knowledge, distrust of in-country drugs or generics.
- Concise, up-to-date information of immediate use is offered.
- Information is limited and key points are repeated; lengthy presentations of new information and reviews will lose the interest of most readers.
- Short headings and visually appealing illustrations are used, so catching the attention of readers.
- The text is brief and simple.
- The information presented is derived from reputable journals, and the references are provided.
- The information provided is orientated towards actions and decisions.
- Feedback from professional staff on the value of the newsletter is asked for and changes made as necessary.
- Local experts are asked to write and comment in order to improve acceptability and credibility.

specific interest at the local level. Drug newsletters are more likely to be effective in improving rational drug use if certain principles are adhered to, as shown in box 7.1.

7.2.4 Formulary manual and standard treatment guidelines

The use of a formulary manual has been shown to be a valuable asset to providing information about drugs to health staff (see section 3.3 and annex 3.2). Likewise manuals or pamphlets on STGs can provide information on diagnosis and treatment (see section 3.4). Like all printed materials they will be more effective if they are pocket-sized, regularly updated and easily available, and accompanied by other more interactive educational strategies.

7.3 Managerial strategies

7.3.1 Developing and implementing standard treatment guidelines

The process of developing and implementing evidence-based STGs can be significantly associated with improved rational use of medicines. Development of guidelines should be participatory, involving end-users, and implementation should be accompanied by training and supervision. For a detailed description see section 3.4.

7.3.2 Audit and feedback

Monitoring drug use and then giving feedback to prescribers on the data collected is a very powerful way to change prescribing behaviour. The steps to follow are described under drug use evaluation (DUE) in section 6.5. Audit and feedback may take several forms and range from the general to the specific, as follows:

- **Monitoring and supervision of drug management** including adherence to the formulary, procurement, storage, distribution, etc., often using aggregate data. Information is fed back to the DTC and relevant departments.
- **Monitoring and supervising prescribing habits** in health facilities before and after an intervention (for example training and supervision) using WHO/INRUD drug use indicators (see boxes 7.3 and 7.4). Information is fed back to all prescribers.
- **Drug use evaluation** is focused on the use of one drug or the treatment of one disease, usually in a hospital. It is an ongoing, systematic, criteria-based programme of drug

evaluations that will help ensure that medicines are used appropriately (see section 6.5). Information is fed back to individual prescribers.

7.3.3 Clinical pharmacy programmes

The utilization of clinically oriented pharmacy personnel to implement drug policies (section 1.3) and other interventions to change drug use behaviour is an important option that is frequently overlooked in many countries. A well-trained clinical pharmacist will have the skills to monitor, evaluate and make recommendations on the use of medicines. Extra payment to hire and retain clinical pharmacists is very worthwhile and will benefit the DTC greatly because such people can:

- help to ensure that indications for medicine use are appropriate
- help to ensure that correct doses are prescribed
- help to ensure that drug interactions and adverse drug reactions are avoided
- ensure that patient counselling/education is provided
- provide prescribers with up-to-date, unbiased drug information
- institute generic substitution and therapeutic interchange programmes where pharmacists are authorized to substitute medicines prescribed by a physician with medicines that are considered therapeutically equivalent. (It is very important that any such policies are agreed to fully by the DTC and medical staff from the outset.)

Generic substitution is the dispensing of a product that is generically equivalent to the prescribed product, with the same active ingredients in the same dosage form, and identical in strength, concentration and route of administration. Since there are many generic products available on the market, often at much lower prices than branded products, generic substitution can result in significant savings in the drug budget. Sometimes generic prescribing and substitution is criticized because of doubts about the bioequivalence of generics, especially if a particular drug is being procured from more than one manufacturer. However, the bioavailability is unlikely to vary significantly between most brand name and generic products if purchasing is done through reliable, registered and pre-qualified suppliers. Nevertheless, it is important to acknowledge clinically important bioavailability problems with generic products where these exist. Important drugs in this category are listed in table 5.2 (see section 5.3.2).

Therapeutic interchange (substitution) is the substitution of one medicine with another that differs in composition but is considered to have similar therapeutic actions and pharmacological activity (including side-effects). Such substitution should only be done in accordance with written protocols previously established and approved. Therapeutically equivalent medicines may include different chemical entities or the same chemical entity in different dosage forms or modes of administration. Therapeutic substitution is especially helpful when newer expensive, patented, single-source drugs are prescribed.

7.3.4 Medicine restrictions

Medicine use and misuse may be controlled by restricting medicine availability:

- **A restricted drug procurement list or an approved formulary** is the most commonly used method to restrict drug availability and to focus on the use of cost-effective and safe drugs (see section 3.2). Such lists are especially valuable for controlling therapeutic groups such as antibiotics, analgesics and psychotropics, where the number of medicines may become excessive because many prescribers have brand preferences and make different choices.

- **A structured drug order form** is a common and successful method used in hospitals to control drug use, especially antibiotics (Avorn et al. 1988). Such a form requires that certain antibiotics or other medicines be prescribed by filling in a pre-printed form which requires certain information to be given. Thus, the specific medicines are pre-printed on the form together with the specific indications for which they may be used and the doses and dose intervals. Prescribers must choose one of the choices offered on the structured order form with regard to drug, indication, dose and dose interval; thus they are guided to prescribe in the most cost-effective way. An example of a structured order form is shown in annex 7.1.
- **Automatic stop orders** are useful for hospital patients and will enforce restrictions on the period of time for which drugs are used. Such orders require that all prescriptions cease after a certain time unless extended. This provides a valuable control on the often unnoticed and unintentional extended use of medicines, especially antibiotics; patients may be left on antibiotics for a long period of time because physicians have neglected to discontinue the medicine.

7.3.5 Avoiding perverse financial incentives

The way hospitals and health facilities charge patients for medicines, particularly in out-patients and pharmacies, may affect the way they are used. Examples include the following:

- Hospital income or prescriber salary depends on the sale of drugs; this can lead to the use of expensive drugs where cheaper ones would be just as good and the inappropriate use of multiple drugs per patient (polypharmacy).
- Flat user fees are charged to patients irrespective of the number or quantity of drugs prescribed and dispensed (for example a registration fee covering all drugs); this can lead to increased patient demand and polypharmacy.

BOX 7.2 THE EFFECTS OF DIFFERENT KINDS OF USER FEE IN NEPAL

A pre-post controlled study of the effects of different kinds of user fees on prescribing quality was conducted in rural Nepal. In 1992 all three study districts charged the same flat fee per prescription. In 1995 the control district charged the same fee, one district charged a single fee per drug item and a second district charged a higher fee per expensive item and a lower fee per cheap item. The item fees covered a complete course for each item. It was found that prescribing quality was significantly better and prescribing costs significantly lower with item fees as compared to a flat prescription fee. All changes were statistically significant ($p<0.025$).

Group	Control flat prescription fee		1-band fee per drug item		2-band fee per drug item	
	1992	1995	1992	1995	1992	1995
Average number of drug items per prescription	2.9	2.9 (0%)	2.9	2.0 (–31%)	2.8	2.2 (–21%)
% of prescriptions conforming to STGs	23.5	26.3 (+2.8%)	31.5	45.0 (+13.5%)	31.2	47.7 (+16.5%)
Average cost per prescription (Nepali Rupees)	24.3	33.0 (+36%)	27.7	28.0 (+1%)	25.6	24.0 (–6%)

Source: Holloway et al. (2001a,b)

The DTC has a role to advise the hospital management or other health authority concerning these issues. If possible, agreement should be established that none of the prescribers has direct financial interest in the health facility pharmacy. Box 7.2 shows how prescribing was affected by user fees in Nepal.

7.4 Regulatory strategies

Adhering to regulatory or statutory requirements is important in attaining rational drug use. A DTC can ensure proper enforcement of regulations within the environment of the health facility.

7.4.1 Supporting national regulations

- **Drug registration**, when enforced properly, will keep ineffective, poor-quality and dangerous medicines off the market and out of the country. Monitoring and enforcing the registration system is important, as otherwise large numbers of unregistered medicines may reach the public and private health-care systems. The DTC should ensure that only registered drugs are used.
- **Professional licensing** of health-care professionals restricts membership of these professions to individuals who are competent and have the necessary training and experience. Licensing can be extended to include level-of-use prescribing, where restrictions are placed on the type of drugs that providers can prescribe depending on their training and experience. The DTC should ensure that only licensed health-care professionals are employed and that their duties comply with national regulations concerning level-of-use prescribing.

7.4.2 Hospital policy on pharmaceutical promotion

Pharmaceutical promotion influences providers at the level of drug selection for the formulary and the choice of drug for individual patients. For many prescribers, drug company representatives are the primary source of information on new medicines. However, their information is often biased since they are primarily salespeople interested in promoting the drugs sold by their companies. Often providers do not realize how they are influenced by promotional materials and activities. Thus providers must be sensitized as to how pharmaceutical promotion can affect their choice of medicines, and trained to analyse the content of promotional materials. Regulating interaction with drug representatives helps the DTC to promote the rational use of medicines and ensure, as far as possible, that the content of materials and information reaching prescribers will be unbiased.

The WHO (1988a) *Ethical criteria for medicinal drug promotion* can serve as a basis for developing measures and guidelines on drug promotion. This document states that 'All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste.'

Regulating drug representatives may be difficult in larger hospitals, or where doctors have active private practices. A DTC may choose to ban representatives entirely, which can be counter-productive as they then approach doctors outside the hospital. One option used in some countries is that of equal time presentations. In this approach representatives are required to submit their materials in advance. The hospital pharmacist or a clinical pharmacologist (if there is one) actively reviews the materials. A meeting is then arranged at which the representative is invited to present his/her information to all doctors, followed by equal time for the pharmacist (or clinical pharmacologist) to comment on the materials presented. Then the meeting can be opened for questions and discussion. By debating the

merits of a new medicine it is possible for prescribers to gain a balanced perspective on that medicine.

Promotional activities may be directed at consumers as well as prescribers. Such promotion may create inappropriate patient demand. A DTC cannot prevent such promotional activities occurring in society at large, but it can ban them in the hospital or facilities under its jurisdiction. For example, a DTC can prevent the display of inappropriate posters, advertising medicines and aimed at consumers, in the hospital or health-care facility.

7.5 Choosing an intervention

The choice of intervention will depend on the type of drug use problem and the reasons why it exists. Not all interventions are equally effective. For example, improving knowledge is often not accompanied by a change in behaviour. Studies have shown that:

- a single-shot educational strategy is usually not very effective and the impact not sustainable.
- the use of printed materials alone is not effective.
- a combination of strategies, particularly of different types, for example an educational one plus a managerial one, always produces better results.
- focused small-group and face-to-face interactive workshops have been shown to be effective, if effective trainers or moderators are used.
- monitoring and feedback and peer review are very effective strategies but require the agreed use of certain standards (for example STGs) against which to judge the prescribing.
- economic incentives can be very powerful ways of changing behaviour; however, poorly thought-out incentives may lead to unexpected behaviour and the promotion of inappropriate use.
- regulatory interventions may have unintended impacts that may be worse than the intended change (substitution of a less appropriate drug for a banned drug, for example).

Box 7.3 summarizes recommended strategies and approaches, and box 7.4 demonstrates the effectiveness of a combined intervention strategy used in Uganda.

7.6 Evaluating interventions

Unless certain study designs are used for data collection when the interventions are implemented, the data will not tell us whether the interventions are effective or not. If we use inappropriate study designs, we will not be able to judge whether observed changes in medicine use are due to our intervention or due to some other factor (a confounder). A detailed description of study designs is beyond the scope of this manual. However, all acceptable study designs include some form of control group, where the intervention is not implemented. The effectiveness of an intervention is judged by comparing medicine use in intervention and non-intervention groups. There are three acceptable study designs:

- randomized controlled trial
- before–after study with control group
- time series.

Sample sizes, as described in section 6.3, i.e. number of prescriptions per prescriber or facilitator and the number of facilities, are important in all designs (except in the case of time series – see below).

BOX 7.3 RECOMMENDED APPROACHES TO PROMOTING MORE RATIONAL USE OF MEDICINES

- Establish procedures for developing, implementing and updating standard treatment guidelines
- Establish procedures for developing, implementing and updating a formulary list based on standard treatment guidelines or treatments of choice and using only registered drugs
- Establish a DTC and define its responsibilities with regard to monitoring drug use, feeding back drug use data to prescribers, and undertaking other activities to promote quality use of medicines
- Employ adequate numbers of licensed staff in roles suitable to their qualifications
- Provide unbiased independent drug information
- Require staff to attend a regular in-service continuing education, which should be face-to-face, targeted, problem-based, and based on standard treatment guidelines, with the input, if possible, of professional societies, universities and the ministry of health
- Stimulate a group process among health providers and/or consumers to review and apply information about appropriate use of medicines
- Train pharmacists and dispensers, including drug sellers to be active members of the health-care team and to offer useful advice to consumers about health and drugs
- Avoid perverse financial incentives.

Adapted from Laing et al. (2001) and WHO (2002c)

BOX 7.4 A COMBINED INTERVENTION STRATEGY IN UGANDA

A randomized controlled trial to test the impact of STGs plus training and supervision on rational prescribing was carried out in Uganda. Prescribing quality, as judged by the percentage of prescriptions (Px) conforming to STGs, did not improve when only guidelines were disseminated, but greatly improved if dissemination of the guidelines was accompanied by training and supervision.

Group	% Px conforming to STG
Control group – no intervention	24.8 → 29.9 (+5.1%)
Dissemination of STG	24.8 → 32.3 (+7.5%)
STG plus on-site training in therapeutic problems	24.0 → 52.0 (+28.0%)
STG plus on-site training in therapeutic problems plus 4 supervisory visits in 6 months	21.4 → 55.2 (+33.8%)

Source: Kafuko et al. (1994)

7.6.1 Randomized controlled trial

This study design is the scientific gold standard. Here the target population (for example patients, health facilities, prescribers) is assigned randomly to receive, or not to receive, the intervention. Data should preferably be collected before and after the intervention from both those who received the intervention and those who did not (control group). Randomization should be performed in a manner which prevents the researchers knowing which treatment subjects will receive (or interventions facilities will receive) as this prevents selection bias (concealed randomization). The assumption is that if the target population is truly chosen randomly, then before the intervention there will be no inherent differences between the intervention and control (non-intervention) groups. Therefore, any observed differences will be due to the intervention and nothing else. This type of study design is often used for clinical trials of drug efficacy, but may also be used for intervention studies to promote rational use of drugs. It is not always possible to conduct a randomized controlled trial for reasons of logistics (for example where the intervention is a regional policy) or ethics (for example non-treatment in the control group).

7.6.2 Non-randomized before–after study with control

In this study design the target population is assigned non-randomly into intervention and control groups and data is collected both before and after the intervention. By taking into account in the analysis any differences between the groups before the intervention, we judge that any differences between the groups observed after the intervention are due to the intervention. The assumption is that any external factors (apart from the intervention) that may have influenced drug use will have influenced both groups equally. This type of study design is often used when evaluating interventions to promote the rational use of drugs in a number of different facilities or areas where a randomized controlled trial is not suitable.

7.6.3 Time series study

This study design involves data collection over a period of time and may or may not include a control group. Ideally data should be collected at least six times before and six times after an intervention, but for pragmatic reasons the minimum number of data collections is often put at four (twice before and twice after the intervention). The assumption is that if observed changes occur in a sustained and consistent manner after an intervention, then they are likely to be due to the intervention. In fact, the baseline trend acts as a 'control' for comparison with the post-intervention 'trend'. This type of study design is used when it is not possible to have a formal control group. In DUE in one hospital, it may be difficult to have a control group since it would be difficult to expose some staff and not others to the intervention. Also, if a DTC is responsible for fewer than 20 health facilities (10 each for intervention and control groups) the number of facilities is insufficient to allow the kind of statistical analysis used in the other study designs.

ANNEX 7.1

Examples of structured order forms from a hospital in Nepal

PATAN HOSPITAL OPD DRUGS

Phcy Use

Patient . . . . . Date : . . . . . .

Hosp no. . . . . Weight . . . . . kg. Age . . . . .

Drug/Strength	Ph. I	Directions	PRICE
1. Actilid	1		
2. Aminophylline 100 mg	28		
3. Antacid	30/50/100		
4. Aspirin 300 mg	30		
5. Amoxycillin 250 mg	21		
6. Chloramphenicol 250 mg	28		
7. Chloramphenicol Ear drops	5 ml		
8. Chlorpheniramine 4 mg	15		
9. Ciprofloxacin 250 mg	10		
10. Clotrimazole Cream 1% 15g/ Pessaries	1/6		
11. Cloxacillin 250 mg	28		
12. Codeine Phosphate 15 mg	12		
13. Cotrimoxazole 480 mg	28		
14. Cough Expectorant	150 mL		
15. Digoxin 0.25 mg	28		
16. Doxycycline 100 mg	8		
17. Ferrous Sulphate 200 mg	28/56		
18. Folic Acid 5 mg	14/28		
19. Frusemide 40 mg	28		
20. Gentamicin Eye/Ear Drops	5 ml		
21. Glibenclamide 5 mg	28		
22. Glycerin	30 mL		
23. Gamma Benzene Hexachloride lotion	100 ml		
24. Hydrochlorothiazide 50 mg	28		
25. Hydrocortisone Cream 1% 15 gm	1		
26. Hyoscine Butylbromide 10 mg	10		
27. Ibuprofen 200 mg	20		
28. Indomethacin 25 mg	21		
29. Magnesium Trisilicate Mixture	500 ml		
30. Mebendazole 100 mg	6		
31. Nalidixic	1		
32. Metronidazole 200 mg	21		
33. Miconazole Cream	15 gm		
34. Multivitamin Tablets	28/56		
35. Neomycin Ointment	10 gm		
36. Neosporin eye Ointment	5 gm		
37. Norfloxacin 400 mg	14		
38. Nystatin Ointment 30 g/ pessaries	1/1		
39. O.R.S. (Jeevan Jal)	1		
40. Paracetamol 500 mg	20		
41. Penicillin V 250 mg	20		
42. Potassium Chloride Syp/tab 500 mg	140 ml/28		
43. Povidone Iodine (Betadine) 5% sol	30 ml		
44. Povidone Iodine 1% Mouth Wash	100 ml		
45. Promethazine theoclate 25 mg	15		
46. Ranitidine 150 mg	14		
47. Salbutamol 2 mg/4 mg / 8mg S.A.	28		
48. Sat Isabgol	100 gm		
49. Savlon 1% Sol.	120 ml		
50. Tinidazole 300 mg	7		
51. Vitamin B Compound	28/56		
52. Whitfields Ointment	30 gm		
53. Gauze/Cotton ball/Pkt	1/1		
54. Gul Dressing set	1		

Clinic	Doctor	HA	Rpt. Rs.	Pharmacy

Form 350 7/058

PATAN HOSPITAL **DISCHARGE DRUGS**

Ph'cy Use

Patient :.... .... Date : .. ..

Hosp no. ....Weight: .... kg Age ... .

NOTE Please Send to Pharmacy at least one hour prior to discharge

	Drug/strength	Pack	Directions	Price
1	Aminophylline 100mg tab	28		
2	Amoxycilin caps 250mg	21		
3	Antacid tab	30		
4	Aspirin 300mg tab	30		
5	Chloramphenicol 250mg cap	20		
6	Chlorpheniramine 4mg tab	15		
7	Ciprofloxacin 250mg tab	10		
8	Cloxacilin 250mg cap	30		
9	Codeine phos 15mg tab	10		
10	Cough Expectorant	150 ml		
11	Darvocet tab	10		
12	Diclofenac SR 100mg tab	10		
13	Digoxin 250 microgram tab	28		
14	Doxycycline 100mg cap	8		
15	Erythromycin 250mg tab	28		
16	Ferrous sulphate 200mg tab	28/56		
17	Folic acid 5mg tab	14/28		
18	Frusemide 40mg tab	28		
19	Glibenclamide 5mg tab	30		
20	Hydrochlorothiazide 50mg tab	28		
21	Ibuprofen 200mg tab	20		
22	Indomethacin 25mg tab	21		
23	Isosorbide dinitrate 10mg tab			
24	Magnesium trisilicate mixture	500 ml		
25	Mebendazole 100mg	6		
26	Metronidazole 200mg	21		
27	Multivitamin tablets	28/56		
28	Neomycin skin ointment	10 g		
29	Neosporin eye & skin oint	5 g		
30	Nifedipine 5mg 10mg SR10mg			
31	Norfloxacin 400mg	14		
32	Nystatin ointment 30g/vag tab			
33	Paracetamol 500mg	20		
34	Penicillin V 250mg tab	20		
35	Potass chloride syr/tab 500mg	40mL/28		
36	Povidone iodine soln	30 ml		
37	Promethazine hcl 25mg tab	10		
38	SFS (Jeevan Jal)	1		
39	Ranitidine 150mg tab	14		
40	Salbutamol 2mg/4mg/8mg5A			
41	Saslon 1% solution	120 mL		
42	Tinidazole 300mg tab	7		
43	Vitamin B complex tab	28/56		

Doctor	Ward	Date	Pharmacy

Form 254 GCH 53

8. Antimicrobials and injections

Summary

Antimicrobials and injectable drugs are amongst the most expensive of all drugs, often consuming most of a hospital's drug budget. In addition to the normal hazards of drug use, the use of antimicrobials contributes to the development of antimicrobial resistance, and poor infection control contributes to the spread of resistant pathogens. Unsafe injections can transmit blood-borne diseases such as hepatitis B and C and HIV/AIDS. Therefore drug and therapeutic committees (DTCs) should:

- monitor the use of antimicrobials and injections to ensure appropriate and safe use
- ensure that appropriate infection control policies and practices are implemented, through an infection control committee or team
- ensure that appropriate surveillance of antimicrobial resistance is conducted in order to inform medicine selection for the formulary list as well as individual patients.

8.1 Antimicrobials, resistance and infection control

Antimicrobials, like any other medicines, may be used inappropriately. A prescriber may choose an inappropriate type of antimicrobial, taking into account the clinical condition, resistance patterns and cost. Incorrect drugs, doses, dose-interval or duration may be prescribed, dispensed or administered. Continuing antimicrobial misuse leads not only to poor patient outcome, unnecessary adverse reactions and wasted resources, but also to emerging resistance of bacteria to antimicrobials. Antimicrobials can also be very expensive, and in most facilities they constitute a major portion of the drug budget. Thus, it is very important for the DTC to pay particular attention to the issue of antimicrobial use.

The phenomenon of resistance is seen not only in bacteria and mycobacteria (multidrug resistant TB, for example), but also in protozoal infections (resistance to chloroquine as an antimalarial) and viral infections (HIV and antiretrovirals). However, for most DTCs the main issue is the use of antimicrobials for bacterial infections.

8.1.1 Problems in the use of antimicrobials

Inappropriate use of antimicrobials is one of the most important types of drug misuse. Often misuse is due to uncertainty about the diagnosis or the identity and drug susceptibility of the organisms. Common areas of misuse particularly associated with antibiotics include:

- treatment of minor respiratory and gastrointestinal infections, viral infections and self-limiting bacterial diseases that do not benefit from use of antimicrobials
- incorrect choice of antimicrobial for common problems, for example the use of a broad-spectrum antimicrobial when a narrow-spectrum agent would be sufficient

- insufficient dose and duration dispensed or purchased because patients cannot afford the cost of the antimicrobial
- inappropriate choice of antimicrobial for surgical prophylaxis
- wrong dose and duration of appropriate antimicrobial prophylaxis and treatment
- the tendency to use newly introduced and expensive antimicrobials, when there is no evidence supporting better drug susceptibility of the newer drug over an older one.

The inappropriate use of antimicrobials is an important factor in the development of resistance. Every time an antimicrobial is used, the susceptible (sensitive) bacteria are killed leaving the resistant ones behind, i.e. the use of antimicrobials selects for resistant bacteria (selection pressure). Antimicrobial resistance is more prevalent in hospital settings than in the community, because of the selection pressure on organisms caused by the high intensity of antimicrobial use. Basic infection control procedures are often not practised, so the transfer of resistant organisms between patients, and between patients and staff, is common. Increasing resistance in the hospital setting contributes to increasing resistance in the community, which is of serious public health importance, since future generations may contract infections that are resistant to treatment.

8.1.2 Improving antimicrobial use and containing resistance

The need for the prudent use of antimicrobials cannot be overemphasized. All the strategies that are used to promote more rational use of medicines generally are also relevant for antimicrobials. Such strategies may be aimed at prescribers, dispensers, those who administer medicines, those responsible for the selection and purchase of medicines, and consumers.

Important strategies to improve antimicrobial use, so containing the development of resistant pathogenic organisms, include:

- An effective antimicrobial subcommittee of the DTC to set norms and monitor antimicrobial use in order to reduce misuse and contain the development of resistant organisms (section 8.1.3).
- Use of antimicrobial treatment guidelines (section 8.1.4) updated according to antimicrobial resistance surveillance data, together with sustained education and supervision on rational use of antimicrobials.
- Classification of antimicrobial prescribing in hospitals into non-restricted, restricted and very restricted to avoid indiscriminate use of antimicrobials of 'last resort' (section 8.1.5).
- Audit of antimicrobial use, by department or by drug, together with feedback and other appropriate measures in order to correct inappropriate use (sections 6.5 on drug use evaluation and 8.1.6).
- Improved diagnostic facilities (section 8.1.7) to aid clinicians not to prescribe antimicrobials unnecessarily, for example malaria blood smear, TB sputum smear.
- Antimicrobial resistance surveillance (section 8.1.10) in order to:
  - — inform clinicians about the susceptibility patterns of bacteria causing infections in individual patients so ensuring correct antimicrobial choice
  - — use the collated information when developing STGs and choosing which antimicrobials should be on the formulary list; this requires the disaggregation of resistance patterns in community-acquired and nosocomial infections
  - — where laboratory facilities are not available, it maybe necessary to rely on surveillance information from the nearest available laboratory in a similar hospital setting. Such

information may be used to identify first-choice antimicrobials which can be used empirically, i.e. without information on the susceptibility patterns of individual patients.

Important strategies to improve infection control, thereby preventing the spread of resistant infections, include:

- An infection control committee (section 8.1.8) to monitor hygiene practices with a view to containing the spread of resistant organisms. The DTC should liaise closely with any existing infection control committee. If no such committee exists, the DTC should form one.
- Guidelines and procedures to prevent the transmission of infections, including those that are drug-resistant (section 8.1.9). There should be policies for hand washing by medical staff when transferring from one patient to another; for using sterile gloves, especially in intensive care wards; and for certain procedures involving the use of disinfectants and sterile equipment.
- Surveillance of infections and antimicrobial resistance (section 8.1.10) in order to detect, and therefore deal with, outbreaks of nosocomial (hospital-acquired) infection.

8.1.3 Antimicrobial subcommittee

The goal of an antimicrobial subcommittee is to assist the DTC in dealing with the management of antimicrobials, and in particular to ensure that:

- Safe, effective, cost-effective antimicrobials are made available.
- Antimicrobials are used only when clinically indicated, at the correct dose and for the appropriate duration of time.
- Correct information is given to patients and that, as far as possible, patients take antimicrobials correctly.

The functions of the antimicrobial subcommittee are similar to those of the DTC, but with an emphasis on antimicrobial drugs. Ideally such a subcommittee would:

- Advise the DTC and medical staff on all aspects of antimicrobial use and misuse.
- Assist in evaluating and selecting antimicrobials for the formulary and standard treatment guidelines.
- Develop policies concerning use of antimicrobials for approval by the DTC and medical staff. Policies should specifically include sections on methods to limit and restrict use of antimicrobials in the hospital and primary care clinics.
- Participate in prescribing quality assurance programmes and drug use evaluations to ensure use of effective antimicrobials of adequate quality only when clinically indicated, in the correct dose and for the appropriate length of time.
- Participate in the educational programmes for health-care staff.
- Liaise with the infection control committee with regard to assessment and use of data obtained from the monitoring of antimicrobial sensitivity and resistance patterns in hospitals and primary care clinics.

8.1.4 Antimicrobial treatment guidelines

Antimicrobial guidelines are a very useful adjunct to the more general STGs and formulary manual. The DTC should be able to develop and advocate the use of antimicrobial guidelines especially for treatment and prophylaxis in the common infections managed in the hospital.

A process similar to that described for STGs (section 3.4) can be used. It is important to emphasize the use of evidence-based information, and assess the local susceptibility patterns. In small hospitals, without laboratory and technical capability, this information should be obtained from the nearest hospitals that do have this capacity and/or are using evidenced-based antimicrobial guidelines. Education on rational use of antimicrobials should include advocacy on the use of the antimicrobial treatment guidelines information and on current antimicrobial susceptibility patterns. A good example of antimicrobial guidelines is contained in a booklet published and used in Australia (Therapeutic Guidelines Ltd 2000).

8.1.5 Classification of antimicrobials

It is important to classify antimicrobials according to the general criteria of efficacy, safety, quality and cost, and according to resistance patterns. Any classification should be country-specific and based on local conditions.

Antimicrobials for non-restricted use

These antimicrobials are safe, effective and reasonably priced (for example benzyl penicillin). All prescribers may prescribe these drugs without approval by senior prescribers or the antimicrobials and infection control subcommittees, but prescriptions should be compliant with STGs.

Restricted antimicrobials

These antimicrobials may be more expensive and/or have a wider spectrum of activity and should only be used for specified more serious clinical conditions (for example, ceftriaxone). Such conditions might include:

- specific infections known to be sensitive to the antimicrobial after culture and susceptibility testing
- empirical emergency treatment of suspected serious or life-threatening infections pending the result of culture and sensitivity testing.
- countersignature by a senior physician who has the approval of the DTC for such an activity.

Thus these antimicrobials are used only with the approval of clinicians who are experts on infectious diseases and familiar with local susceptibility patterns.

Very restricted

These antimicrobials should be reserved for life-threatening infections (for example, vancomycin). They should only be used when culture and sensitivity testing has indicated resistance to other effective and less expensive antimicrobials. Approval for use in each individual patient must be given by the clinical microbiologist or the DTC itself.

In hospitals without laboratories, it may not be possible to distinguish between 'restricted' and 'very restricted' and the two categories may be treated as one.

8.1.6 Antimicrobial use review

This is the same as drug utilization evaluation (DUE) or an audit and feedback programme where the drug being evaluated is an antimicrobial. The steps involved in conducting such a review are the same as for DUE, and are demonstrated in the country example shown in box 8.1. Antimicrobial use audit should be done at regular intervals to make sure that

prescribers adhere to the hospital antimicrobial policy and guidelines. Medicines given during the discharge of inpatients and those prescribed to outpatients should be monitored in order to contain the spread of antimicrobial-resistant bacteria to the community.

8.1.7 Improved diagnostic facilities

Many antimicrobials are prescribed unnecessarily because the prescriber is unsure of the diagnosis. Diagnostic procedures can help to ensure that antimicrobials are prescribed only when needed. For example, using malaria blood smears in hospitals helps to ensure that patients with malaria are treated with antimalarials and not with unnecessary antimicrobials. Sputum microscopy for TB helps to ensure that those patients with TB are treated with antitubercular drugs and not with inappropriate antibiotics. As for any laboratory procedures, quality control for diagnostic procedures and microscopy is vital as otherwise false diagnoses will be made or true diagnoses missed (see section 8.1.10 on antimicrobial resistance surveillance).

8.1.8 Infection control committee

The goal of an infection control committee is to prevent the spread of infection within the hospital or facilities within its jurisdiction. This involves overseeing the hospital's infection control, prevention, and monitoring programmes (Wenzel et al. 1998). An infection control committee usually operates independently of the DTC, but will frequently rely on the DTC's advisory function. Where there is no such committee, the DTC should create a subcommittee that will specifically deal with all issues relating to infection control. If there are not sufficient professional staff in a hospital, the infection control committee could be combined with the antimicrobial subcommittee. In any case better coordination would be achieved by some overlap of membership between the infection control and antimicrobial subcommittees. If there are still fewer personnel, as is the case in many small hospitals in developing countries, coordination with bigger hospitals and professional groups specializing in infectious diseases will be necessary. What is crucial is that somebody is responsible for ensuring that infection control procedures and strategies to prevent unnecessary antimicrobial use are in place.

The functions of an infection control committee are concerned with environmental issues such as food handling, laundry handling, cleaning procedures, visitation policies and direct patient care practices, including hand washing and immunizations. An infection control committee should:

- Carry out active surveillance of infections and antimicrobial resistance, with data analysis and feedback (ideally monthly reports) to the appropriate departments, health-care staff, antimicrobial subcommittee and the DTC.
- Develop and recommend policies and procedures pertaining to infection control.
- Intervene directly to prevent infections.
- Recognize and investigate outbreaks or clusters of infections.
- Educate and train health-care workers, patients and non-medical care-givers.

Normally the infection control committee appoints a team, often just one nurse in small hospitals, to implement its policies. Where there are laboratory facilities a microbiologist is responsible for collating and assessing sensitivity and resistance patterns.

BOX 8.1 ANTIMICROBIAL REVIEW IN KENYA

The DTC in a Kenyan hospital decided to undertake a drug use evaluation of amoxycillin. It decided on the following criteria:

- Acceptable indications are upper/lower respiratory tract infections, genitourinary infections, septicaemia, surgical prophylaxis, skin and soft tissues infection, osteomyelitis, peritonitis
- Acceptable dosage is usually 250 mg three times daily; dosage may be doubled in severe infections
- Acceptable duration is usually 5 days; duration may be doubled in severe infections.
- Total cost for dosage for 5 days = Kenya Shilling (KSH) 470. This includes the dispensing fee of KSH 240

The worksheet below shows the treatment with amoxycillin of 10 patients by one prescriber.

Indications

Patient 1 tonsillitis
Patient 2 otitis media
Patient 3 urethritis
Patient 4 bowel sterilization
Patient 5 severe gram-negative meningitis
Patient 6 boils, abscess
Patient 7 severe cystitis
Patient 8 surgical prophylaxis
Patient 9 pneumonia
Patient 10 severe wound infection

Review criteria for DTC	Patients									
	1	2	3	4	5	6	7	8	9	10
Appropriate indication?	yes	yes	yes	no	no	yes	yes	yes	yes	yes
Amoxycillin dosage (mg 3 x daily)	250	250	250	[a]	500	250	500	250	250	500
Duration (days) (usually 5 days)	5	7	7	1	10	7	5	5	5	7
Cost per capsule (KSH)	30	30	30	30	30	30	30	30	30	30
Total cost (KSH)	470	650	650	380	1800	650	920	470	470	1280

[a] Dosage prescribed was 1500 mg 2 x daily.

On analysis, it was concluded that:

- Patients 4 and 5 were prescribed amoxycillin inappropriately. Bowel sterilization would require a long-acting sulfonamide or neomycin tablets and severe gram-negative meningitis would need a cephalosporin
- Patients 2, 3, 6 and 10 were prescribed 7 days instead of 5 days
- Frequency of prescribing for the wrong indication: 2/10 = 20%, cost = Ksh 380 + 1800 = 2180
- Frequency of prescribing unnecessarily long duration: 4/8 = 50%, cost: 2 capsules in each of 4 patients = 60 x 4 = Ksh 240
- Total costs due to inappropriate prescribing = Ksh 2180 + 240 = 2420 = 31% of the total costs

Source: *MSH* 1997, chapter 31, p. 475.

8.1.9 Preventing the transmission of infections

Preventing transmission of infections helps not only to prevent healthy individuals from becoming ill but also to contain resistance. Firstly, one can reduce the spread of resistant bacteria and, secondly, one can reduce the need to treat sensitive infections with antimicrobials, thereby reducing selection pressure for resistant organisms. The infection control committee is responsible for undertaking active surveillance of infections and antimicrobial resistance, and for developing policies to ensure implementation of the following activities to minimize the spread of infection:

- hand washing by staff between patients and before undertaking any procedures, for example injections
- use of barrier precautions, for example wearing gloves and gowns for certain agreed procedures
- adequate sterilization and disinfection of supplies and equipment
- use of sterile techniques, together with protocols, for medical and nursing procedures, for example bladder catheterization, administration of injections, insertion of intravenous cannulas, use of respirators, sterilization of equipment, and other surgical procedures
- maintenance of appropriate disinfection or sanitary control of the hospital environment, including:
  - — adequate ventilation
  - — cleaning of the wards, operating theatre, laundry, etc.
  - — provision of adequate water supply and sanitation
  - — safe food handling
  - — safe disposal of infectious equipment, for example dirty needles
  - — safe disposal of infectious body fluids, for example sputum
- isolation of infectious patients from other non-infected patients, for example separation of suspected and proven sputum-positive TB cases
- visitation policies, for example preventing visitors with coughs and colds visiting patients who may be immunocompromised, for example patients with AIDS or leukaemia, or premature babies
- training of health-care staff in appropriate sterile techniques and infection control procedures
- immunizations
  - — routine childhood vaccinations in the community, for example diptheria, tetanus, polio, pertussis, measles, BCG, *Haemophilus influenzae*
  - — vaccination of community members and staff in times of threatened epidemics, for example meningitis, typhoid, influenza
- patient education in hospitals or health facilities on topics that may help to reduce transmission of infections in the community, for example:
  - — hygiene, hand washing, safe water and sanitation – to prevent diarrhoeal disease
  - — immunization – to prevent diptheria, measles
  - — bednets – to prevent malaria
  - — condoms – to prevent sexually transmitted diseases and HIV.

8.1.10 Antimicrobial resistance surveillance

The extent of resistance discovered by laboratory culture and sensitivity testing is only the tip of the iceberg in terms of the total bacterial strains and antimicrobial resistance that may be present in the community. Of all the people exposed to resistant organisms, only some will become infected; of infected patients, only some will manifest disease; of diseased patients, only some will seek medical attention; of those seeking medical attention, only some will give a clinical specimen; in only some specimens will a pathogen be isolated; and only for some pathogens will resistance be tested.

Surveillance of bacterial resistance to antimicrobials is an essential component of any programme to contain the spread of resistance. Only by knowing the extent of the problem can appropriate choices be made and staff persuaded to change their use of medcines. Resistance data not only help in choosing the correct antimicrobial in individual patient care; they also, if collated, allow a DTC to be informed about sensitivity patterns when choosing antimicrobials for the formulary. Many hospital laboratories do not actually collate resistance data in order to inform the formulary process, but the DTC has a role in ensuring that such information is provided if possible.

Often resistance is reported in terms of the number of isolates. However, such data usually include multiple specimens from a few very sick patients and does not give an accurate picture of overall resistance in all patients. In order to inform the formulary process, resistance data should be representative of all likely patients, and therefore the data should be collated by case (or patient) not by isolate. If specimens for culture are taken from patients on arrival at a hospital, before they receive any antibiotics, the resulting data may be used to gain an impression of resistance patterns in the community.

Detailed discussion about resistance surveillance is beyond the scope of this manual. However, if surveillance is done, quality control within the laboratory is extremely important. It is worse to have inaccurate reports than none at all. Any good and reliable microbiology laboratory should be able to demonstrate to the DTC documented internal and external quality assurance:

- **Internal quality assurance** consists of regularly conducting and recording various internal checks to ensure that all laboratory equipment is functioning and that all specimen collection and processing is done in a reliable manner.
- **External quality assurance** is where the laboratory participates in an external scheme run by a reference laboratory. In such a scheme, the reference laboratory sends out test clinical specimens, and asks the participating laboratory to identify the organism and its sensitivity pattern. In this way the competence of the participating laboratory can be checked against that of the reference laboratory.

Box 8.2 shows a checklist of questions that a DTC may ask of a microbiology laboratory in order to make an assessment of its likely quality and reliability with regard to the isolation and identification of bacteria and sensitivity testing to antimicrobials.

8.2 Safe and appropriate use of injections

Injections are used inappropriately just as antimicrobials and other drugs are. In addition to the usual hazards associated with inappropriate medicine use (poor patient outcome, wastage of resources and unnecessary adverse effects), inappropriate injections are also associated with the extra risk of disease transmission due to non-sterile equipment and technique. Hepatitis B and C and HIV are commonly transmitted by injection. Furthermore, injections are more expensive than many oral medicines. Thus, it is very important for the

BOX 8.2 CHECKLIST TO ASSESS THE RELIABILITY OF A MICROBIOLOGY LABORATORY

1 Laboratory facility

- What percentage of the day are the following services available:
  - — regular running water (necessary for cleaning equipment)?
  - — electricity (necessary for running incubators, fridges and freezers)?
  - — gas (including bottled)?
- Is there a back-up power source? If yes, what systems are protected?
  - — refrigerators? ventilation/air conditioning? computers? incubators? other?
- What ventilation is provided?
  - — windows?
  - — electrically-powered ventilation system (exhaust, not fans) or air conditioning?
- Is the laboratory clean?
- Does the laboratory appear to be well organized?
- Are the activities – (1) washing/sterilizing equipment, (2) specimen processing and (3) waste disposal – done in clearly separate locations?
- What is the workload of the staff?
- Is there a 24-hour service? If not, what are the hours of service?
- What proportion of the time is a trained microbiologist supervising the laboratory?
- Has training been conducted for laboratory staff in the past year?
- Are safety procedures in place and are they implemented?
  - — is waste disposal adequate?
  - — are documented standard operating procedures and safety manual available?
  - — are protective clothing and equipment for staff, for example latex and other gloves, lab coats, safety visors and glasses available?

2 Equipment

Is all the appropriate equipment present?

Capital equipment

- Refrigerators (+4 °C) and freezers (–20 °C)
- Optical microscope with oil immersion objective
- Scale or balance
- Candle jars or an anaerobe jar
- Bunsen burner or electric heater or alcohol lamp to sterilize loops and needles
- pH meter and pH paper
- Staining facilities – sink and slide rack
- Manual pipettes and pipette washers (if pipettes not disposable)
- Water distillation system (or distilled water)
- Centrifuge (hand or electrically powered)

Continued

BOX 8.2 CONTINUED

- Autoclave – manually controlled and electrically controlled
- Hot air oven
- Electrically-powered water-bath
- Warm air incubator (for culture) with temperature monitor
- CO_2 incubator and CO_2 tanks

Recurrent equipment

- Slides, cover slips
- Loop/needle handles, 0.01 and 0.001 ml calibrated loops
- Petri dishes – disposable or glass
- Test-tubes and test-tube racks
- Adequate glassware for media preparation (flasks, graduated cylinders, etc.)
- Wash bottles

Is all the equipment functioning and is this routinely monitored and recorded?

- Microscope calibration
- Checking the temperatures of refrigerators, freezers and incubators
- Calibration of pipettes, handling devices, autoclave function, balances
- Is there an emergency generator to maintain the power supply?

3 Reagents for bacterial culture, isolation, identification and sensitivity (discs) testing

- Where are reagents procured? a commercial supplier? another lab? prepared in-house?
- Are the reagents stored and labelled appropriately?
- Do the reagents have expiry dates? What percentage are expired?
- What type of water is used for preparation of media and reagents?
  - — deionized? distilled? distilled and deionized? tap water?

4 Specimen collection

- Are all specimens labelled with the patient's name, location, a unique identifier and the time of collection?
- Are all specimens accompanied by a form stating the patient details and tests required?
- Are there protocols for specific specimen collection? If yes:
  - — Are they available to all staff (for example in wards and in outpatients)?
  - — Are they followed and is this documented?
  - — Are adequate sterile collection procedures and transport media used?

Continued

BOX 8.2 *CONTINUED*

- Are specimen transport and storage times and temperatures satisfactory? These times will vary, e.g:

Specimen type	Transport	Storage
midstream urine in sterile container	<2 hours RT[a]	<24 hours 4 ˚C
sputum expectorate in sterile container	<2 hours RT	<24 hours 4 ˚C
urethral/genital/cervical specimen in transport swab	<2 hours RT	<24 hours RT
abscess pus in transport swab	<2 hours RT	<24 hours RT
faeces in sterile container	<1 hour RT	<24 hours 4 ˚C
blood culture in culture vials	<1 hour RT	<24 hours RT
cerebrospinal fluid in sterile container	<15 min RT	<24 hours RT
conjunctival specimen in transport media	<15 min RT	<24 hours RT

[a] RT, room temperature

5 Processing specimens in the laboratory

- Are there manuals for test procedures, internal quality control, safety and safe waste disposal? Have they been updated in the last 5 years?
- Are samples of culture media regularly checked for sterility? What percentage are found not to be sterile?
- Are known bacterial strains regularly grown on samples of culture media to ensure the quality of the culture media? What percentage of samples do not grow the expected strain?
- Are known bacterial strains with known susceptibility patterns regularly grown and checked against samples of antibiotic discs in order to ensure the quality of the discs? What % of samples do not show the expected susceptibility pattern?
- Are isolation rates of bacteria monitored, analysed and appropriate action taken?
  - — Changes in isolation rates may be due to a problem in processing the specimens
  - — Certain bacteria are difficult to grow and may be very dependent upon processing, for example quality of transport media (*Vibrio cholerae*), incubation temperature (*Haemophilus influenzae*), shorter specimen transport time than usual (<15 min for *Neisseria meningitidis*)
  - — Lower isolation rates as compared to previously, or to other similar hospitals, may be due to laboratory processing problems, not lower rates of infection
  - — Higher isolation rates with different bacteria as compared to previously or to similar hospitals may be due contaminants or overgrowth of bacteria due to laboratory processing problems, not higher rates of infection
- Are specimens sent to other institutions for processing?
- Is there timely reporting of individual specimen results to staff and patients?
- Is there periodic reporting of sensitivity test results to clinical staff and the DTC or an antimicrobial subcommittee of the DTC?

Adapted from Murray et al. (1995) and WHO (2001).

DTC to pay particular attention to whether injections are used appropriately and whether injection practices are safe.

Inappropriate use of injections is a very important kind of drug misuse. Often injections are used when oral drugs could be used. In many countries, both prescribers and patients believe that injections are 'stronger' and work faster than oral drugs. Prescribers often complain that they prescribe injections unnecessarily because of patient demand, whereas patients often say that it is the prescribers who wish to give injections. Uncertainty about the diagnosis and likely patient outcome probably contributes to overuse of injections. Strategies to promote more rational, safe use of injections are similar in the main to those used for promoting rational use of drugs in general, and antimicrobials, including infection control, in particular. Box 8.3 describes an intervention strategy used in Indonesia to reduce the overuse of injections.

BOX 8.3 IMPROVING THE USE OF INJECTIONS IN INDONESIA

A study carried out by the Ministry of Health in Indonesia in 1988 found various types of inappropriate drug use including overuse of injections. Focus group discussions found that prescribers often gave injections because they felt that patients demanded them, but that patients in fact preferred oral medications. It was hypothesized that an interactional group discussion focusing on the discrepancies between prescribers' and consumers' perspectives might result in a reduced use of injections. In 1992 a randomized control trial of a group process intervention to reduce injection use was conducted in one district, involving 24 health centres, 12 receiving the intervention and 12 acting as controls. The group process involved a facilitated 2-hour discussion between health workers and the community concerning the use of injections. In the group discussion, health workers' beliefs that patients demanded injections and patients' beliefs that they did not demand injections, were shared. This intervention resulted in a significant reduction in injection use ($p < 0.025$) and the number of items prescribed per patient ($p < 0.025$) over 6 months. This improvement was sustained over the next 2 years.

Group	Control	Facilitated discussion
Number of drug items per prescription	3.97 → 3.88 (–2.3%)	4.03 → 3.67 (–8.9%)
% prescriptions with injections	75.6 → 67.1 (–8.5%)	69.5 → 42.3 (–27.2%)

Source: Hadiyono et al. (1996)

In addition to general strategies to promote more rational use of medicines, the safe and appropriate use of injections requires the safe disposal of used syringes and needles. Strategies particularly concerned with injection overuse include:

1. **An injection subcommittee of the DTC**, with the following tasks:
   - **Monitor injection use and its appropriateness** – this may involve using the WHO/INRUD indicators (WHO 1993), monitoring monthly syringe or needle use, or a more specific injection utilization review.
   - **Ensure the availability of appropriate equipment in sufficient quantity**. Preferably, disposable syringes and needles should be used if there is sufficient money. If re-sterilizable syringes and needles are used, the DTC must ensure that adequate sterilizing equipment is available (steam sterilizer) and that documented monitoring and supervision is undertaken to ensure safe injection practices. Attention should be given to matching the quantities ordered of syringes and needles with injectable drugs. For example, the number of disposable syringes and needles ordered should

match the total number of injection doses ordered; the number of sterilizable syringes and needles should be sufficient for one syringe and needle per patient per day (or other interval between re-sterilization).

- **Ensure adequate disposal facilities**; this includes sharps boxes in clinical areas and access of the health facility to a waste disposal pit or incinerator.
- **Educate prescribers with regard to safe, appropriate injections**
  - — prescribe oral drugs whenever possible
  - — use one syringe and needle per patient, taken either new from a sterile unbroken package or directly from a sterile area
  - — without recapping, place syringes and needles in a safety box immediately after use
  - — manage waste safely and appropriately.
- **Educate patients with regard to safe, appropriate injections**, for example
  - — take oral drugs, and not injections, wherever possible
  - — accept injections only from trained personnel
  - — accept an injection only if the needle and syringe are taken from a new sealed package or (if reusable) from a clean sterile container.

2. **An infection control committee** with the following tasks:
   - **Monitor the safety of injection use** with regard to:
     - — sterilization of equipment
     - — sterile technique in administration
     - — safe disposal of equipment.
   - **Train and regularly supervise staff** in sterilizing equipment, using a sterile technique for administration and safe disposal.
   - **Recognize and investigate outbreaks of adverse reactions associated with injection delivery**, and take appropriate corrective action.

In large hospitals there can be a separate DTC, injection subcommittee and infection control committee, as may also be the case for antibiotics (see section 8.1). However, in many smaller hospitals, there may only be sufficient personnel for a DTC and infection control committee, or only a DTC. Such small hospitals should liaise with bigger hospitals and professional groups on issues of infection control. It does not matter exactly which committee undertakes these functions, but it is the DTC's responsibility to ensure that the activities are undertaken. Box 8.4 shows a checklist used by supervisors in assessing injection safety in Uganda.

BOX 8.4 CHECKLIST FOR ASSESSMENT OF SAFE INJECTIONS IN UGANDA

Before administration

- Are reusable syringes and needles flushed with water after use and before sterilization?
- Is steam sterilization done at the correct temperature (121 °C) for 15 minutes?
- Is equipment boiled for 20 minutes after the last contaminated piece of equipment is put into the boiling water?
- Are only sterile solutions injected?
- Are hands washed with soap?
- Are the rubber tops of ampoules/vials disinfected?

During administration

- Can anything not in an aseptic condition contaminate the injection fluid?
- Does the person injecting touch the needle with his/her finger?
- Does the needle come into contact with any other non aseptic surface?
- Are several patients injected with the same needle?
- Are several patients treated with the same syringe?

After administration

- Are disposable syringes and needles placed into a final disposal container?
- Are disposables recapped before disposal?
- Are disposable syringes and needles disposed of and not reused?
- Are patients observed for about 30 minutes after injection?
- Are sterilizable syringes and needles flushed with water after use?

Source: WHO (1994b)

9. Getting started

Summary

DTCs can nearly always be started or their functioning improved by demonstrating a drug use problem to all the major stakeholders and senior prescribers and then planning with them what do to about it. The plan should include:

- measuring the problem quantitatively
- investigating the problem qualitatively to understand underlying reasons for the problem
- developing and implementing an intervention to correct the problem
- measuring the drug use problem again in order to evaluate the intervention.

The problem of a DTC not functioning can be dealt with in the same way. Firstly, the aspects that are not working need to be defined, secondly, the reasons that this is so investigated and finally, an appropriate intervention developed and implemented. Getting a DTC started will require a strategy based on:

- local conditions
- local data
- starting small and scaling up
- choosing a problem that can easily be addressed
- transparent decision-making
- political and administrative support.

9.1 Addressing the problem

A DTC must deal with many issues but it cannot do so all at the same time, especially in the beginning. The way to get started will depend on the varying circumstances and context in different countries, health-care systems and hospitals. Many countries do not have DTCs in their hospitals or facilities. In other countries where DTCs do exist, many of them do not function properly.

Any process of change requires, first, that someone realizes the need for change. In the context of DTCs, the first step is for **you**, the reader, to realize that irrational drug use is a problem and that a DTC may provide a framework for solving the problem in your own environment. Thereafter, your job is to convince others of the need to address the problem of irrational drug use and to work with them in finding the solutions through a DTC. This chapter is designed to help you get started and shows how to use this manual in the process. Three areas are covered:

- how to start a DTC where none exists
- how to improve the functioning of an existing DTC
- how to use this manual in solving problems.

9.2 Stepwise approach to starting a DTC where none exists

STEP 1 Do your groundwork

Starting a DTC will require you to undertake a lot of advocacy. For this you will be better prepared if you have gathered your evidence. Some questions to ask yourself and others include:

- Are there any data on medicine use problems? If so, collect them.
- Do senior staff (doctors, pharmacists, nurses) think there are problems, and if so what are they? Reported problems might include:
  - — prescription of too many medicines (section 6.3)
  - — overuse of antibiotics or injections (section 6.3 and chapter 8)
  - — medication errors (section 5.2)
  - — medicines not working (section 5.3 and chapter 4)
  - — poor quality drugs (section 5.3)
  - — adverse drug reactions (section 5.4)
  - — frequent drug stock-outs due to insufficient budget (chapter 3)
  - — frequent drug stock-outs due to poor supply system (chapter 3)
  - — drugs not on the formulary list (section 3.2)
  - — prescribers not following the formulary list (section 3.2.5)
- Which problem do staff feel is the most serious?
- How do staff think these problems, and especially the most serious one, should be addressed?
- Of the most serious problems, which one could be addressed most easily?

STEP 2 Gain a friend in authority

Take the findings of your initial groundwork to the most senior medical authority that you can find, and discuss what he or she thinks. Present any data you may have collected and discuss how it might negatively affect patient outcome and/or increase the hospital (or health facility) budget. Discuss how improved use of medicines could lead to improved patient outcomes and/or decreased costs. Plan a course of action with this senior medical person. This course of action may include:

- meeting with all medical staff to identify a problem to investigate, or
- initial investigation of a drug use problem to discuss later with medical staff.

STEP 3 Meet all the senior staff and stakeholders

With the approval of senior management, meet all senior health staff to discuss medicine use problems. In your initial meeting you may:

- present the findings of your groundwork
- present any extra drug use data, for example ABC analysis, that you may have done, following your meeting with the most senior medical authority.

Then:

- If all agree that drug use problems are a serious issue, ask them how they wish to address it – **this is your first opportunity to discuss having a DTC**.
- If they do not agree that drug use problems are serious enough to warrant a DTC, get agreement from them to investigate a drug use problem of their choice.

If prescribers are involved at the start of a project to investigate a drug use problem, they are more likely to accept the results. In any case, certain detailed investigations such as drug use evaluation (DUE) cannot be done without the cooperation and participation of senior physicians. It is wise to choose one of the simpler problems for which you can see a solution rather than a more complex problem which has no easy answer. You need this first investigation to be a success so that you can use it later to advocate for having a DTC.

STEP 4 Measure your medicine use problem

Measuring a specific problem in detail is your first step to improving medicine use. What you will investigate will depend on what the agreed problem is. One possible approach that may address problems of the formulary list, stock-outs and overuse might consist of the following steps:

- involve all the senior staff in a VEN analysis to identify vital, essential and non-essential drugs.
- conduct an ABC analysis to identify which drugs consume most of the budget (A drugs).
- compare the VEN and ABC analyses to see whether any non-essential drugs are in the high cost/consumption A category.

STEP 5 Present your findings and plan next steps with your stakeholders

Present the results of your investigation to all the stakeholders. During the presentation, you can mention how much time it took and thank all those who helped or participated. Assuming some drug use problems are identified, discuss with the group:

- what they think of the findings; try to get a consensus from them on which are the most important problems
- how to address the drug use problems identified – **this is your second opportunity to discuss having a DTC**
- a plan for a more detailed investigation of the drug use problem chosen in order to find out how best to rectify the problem.

Whether or not the group agrees to discuss having a DTC, do not lose the momentum in trying to promote more rational use of medicines. After VEN/ABC analysis the next step is to discuss with the group the nature of the problem, its size, why it exists and what to do about it. If the causes are well understood and agreed, then solutions can be found by the group. If not, then the group should agree to a process of more detailed investigation (see next step).

Even though the stakeholders' meeting is not a DTC meeting, it presents an opportunity to give people the idea of how a DTC might function. Thus, minutes should be recorded. It may be necessary to write up a small proposal for conducting any agreed drug use investigation and submit it to the hospital or regional administrative authority, requesting funds and human resources. The involvement of the senior prescribers and stakeholders from the meeting will lead to greater cooperation and acceptance of the findings and also understanding of the work involved.

STEP 6 Undertake a detailed drug use investigation

The type of study will depend on what the drug use problem is and the type of facility. It may be necessary to write up a small proposal and circulate it to the members of the stakeholder/prescriber group and the hospital administration before conducting the study. Make sure you cover the issues of human resources and finance to conduct the investigation. Extra staff may need to be hired, or at least existing staff excused from certain activities in order to do the study.

In a hospital, a DUE of one or two drugs may be done, choosing a drug according to whether it:

- has the highest value
- has serious side-effects
- is non-essential
- has more consumption than expected from morbidity patterns.

In primary health-care facilities, an indicator study may be more appropriate. In both cases, some qualitative investigation is needed to find out the reasons underlying the prescribing behaviour. The final choice of which type of investigation to do should be that of the group.

STEP 7 Present your detailed findings and plan an intervention

Present the results of your detailed investigation to all the stakeholders in a meeting and also by report to the hospital administration. During the presentation, you can mention how much time it took and thank all those who helped or participated. Discuss and agree with the senior prescribers and stakeholders in the group a plan of action which may include:

- a targeted intervention based on the detailed study findings
- initiating a formulary process or other general means to improve medicine use – **this is your third opportunity to discuss having a DTC**.

STEP 8 Implement and evaluate an intervention to correct the problem

Implement the intervention and evaluate it by measuring the drug use problem before and after implementation. Interventions may be educational, managerial or regulatory (chapter 7) and should be implemented with the full cooperation and participation of the senior prescribers and stakeholders. Measure also the cost of the intervention and the savings in terms of less drugs used as hospital administrators are likely to be more supportive in the future if they see that your measures have saved money. The type of interventions used will depend on the nature of drug use problem identified and investigated. Section 9.4. summarizes a number of problems, causes and suggested solutions.

STEP 9 Present the results of your intervention to senior prescribers

The final step of any intervention study is to present the findings to the interested stakeholders – prescribers and senior management. In fact, if the senior prescribers have been fully involved, they will already know the results and be keen to spread them to all other prescribers. During this dissemination, the following need to be emphasized:

- the benefits – improved health care for patients and reduced costs for the hospital or health facilities

- the need for time and resources to achieve an improved result
- The need for a sustainable mechanism to conduct such work – **this is your fourth opportunity to discuss having a DTC**.

STEP 10 Plan the start of a DTC

If the above process has been followed, it is very likely that you will already have started planning a DTC. If not, a successful intervention may gain the support you need to do so. By now, your senior friend in authority, whom you have kept fully involved in the process, should be sufficiently motivated to help in the establishment of a DTC. Terms of reference, membership and methods of working need to be agreed by the senior physicians and management (chapter 2). A successful DTC is an active one. Therefore, the cycle of changing drug use problems should be continued, addressing one drug problem at a time.

9.3 Revitalizing non-functioning DTCs

Many DTCs do not function. The way to address this is very similar to starting up a DTC from scratch. Often DTCs do not function because there is:

- lack of awareness of drug use problems or interest to address these problems
- lack of awareness of what a DTC could do to address drug use problems
- lack of time or reward for members to undertake any DTC activities
- no mandate or support from senior authority.

Just as with changing medicine use problems, the first step is to quantify the problem and understand why it exists. Only after this can solutions be found. Therefore, if staff are unaware of medicine use problems, demonstrate the problems and their underlying causes. If DTC members are not active, find out why. Perhaps DTC members are not given sufficient reward for their effort and you need to find suitable incentives – this will mean gaining the support of the senior administration. Perhaps DTC members have a conflict of interest and do not want to be active. In such a case, you would need to gain senior support for introducing regulations concerning conflict of interest in DTC members. Finding such support is likely to require evidence of drug misuse, for example the unnecessary cost of using a more expensive branded product which is no more effective or safe than a cheaper alternative.

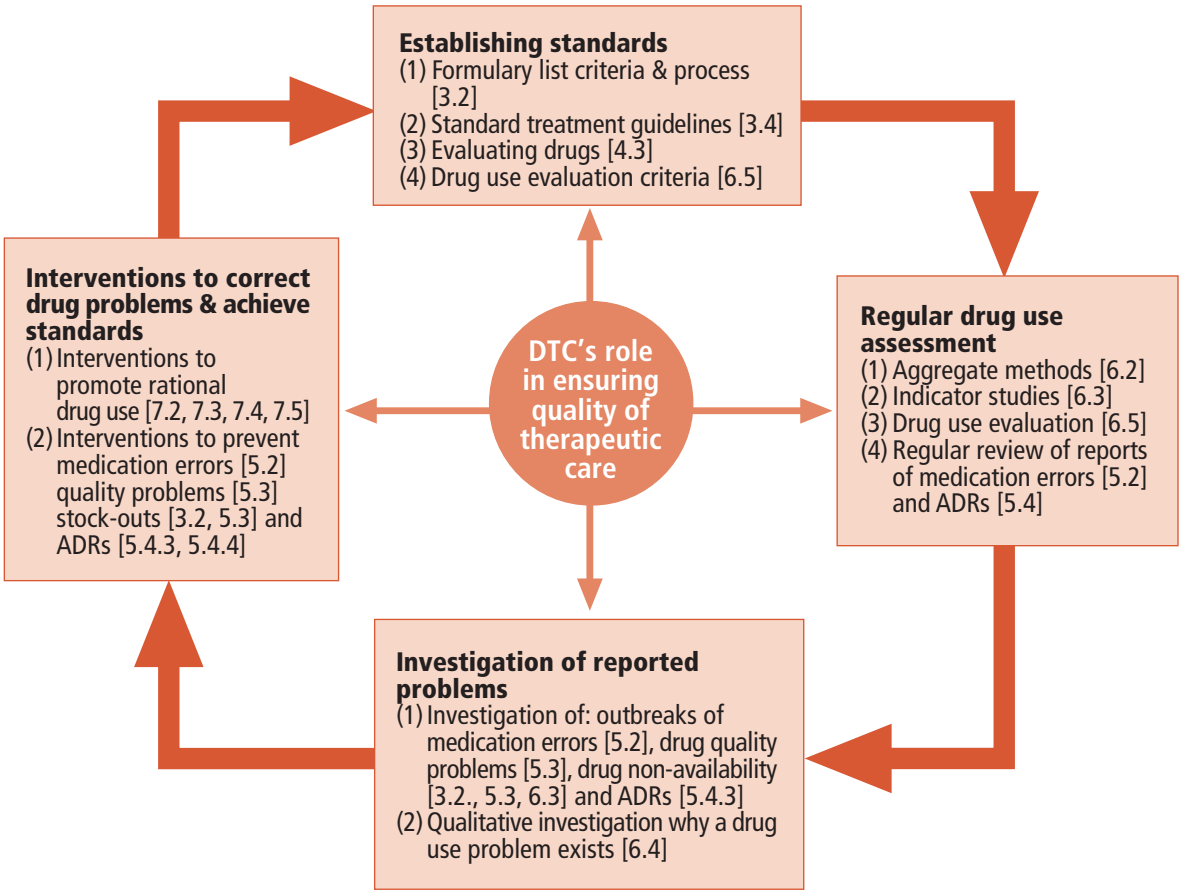
If a DTC has ceased to function because a specific issue cannot be resolved, for example a decision about a formulary medicine, investigate whether all the appropriate steps had been taken. If not, tackle the problem again following an agreed set of steps (as suggested in this manual). If all the correct steps had been followed, or could not be followed because of reasons beyond your control, then leave this problem and choose a simpler one to solve first. Resolve the simpler problems before tackling the more complex ones.

9.4 Using this manual to solve problems

The goal of a DTC is to ensure that patients are provided with the best possible quality of therapeutic care. Every country and health institution in the world has problems of medicine use. Thus, a DTC should always be looking for drug use problems and then trying to solve them. If we do not look for problems we will not find them, but that does not mean they do not exist. Figure 9.1 shows the role of the DTC in maintaining quality of care.

There will be no one solution or starting point for every hospital DTC. What you do will depend on your local circumstances. The activities of a DTC should be problem-based –

Figure 9.1 **The DTC and quality of care**



always looking for problems and finding solutions. Table 9.1 summarizes possible problems, causes, solutions and the relevant section in the manual.

It is not the role of the DTC to take over the function of any department. The membership of the DTC should be drawn from the various departments and their expertise used to ensure that all aspects of drug management and use are performed to a high level in a coordinated manner.

In conclusion, getting a DTC started or making it more functional will require a strategy based on:

- local conditions
- local data
- starting small and then scaling up
- choosing a problem that can easily be addressed
- transparent decision-making
- political and administrative support.

There is nearly always something we can do to get started. Patients deserve all our effort to ensure that they receive drugs appropriate to their clinical needs in doses that meet their individual requirements.

Table 9.1 **Examples of problems, causes and solutions**

Problem and causes	Solutions	Section
Formulary list not followed		
No formulary list	Develop a formulary list	3.2.2
Prescribers do not know about formulary list	Distribute the formulary list	3.2.5
Prescribers do not believe in formulary list	Involve prescribers in development of a formulary list	3.2.2, 3.2.3
Inconsistency between the formulary list and standard treatment guidelines (STGs)	Review the formulary list to make it consistent with the STGs	3.2.4
STGs not followed		
No STGs exist, or they are outdated	Develop STGs	3.4.1
Prescribers do not know about the STGs	Distribute STGs	3.4.2
Prescribers do not believe in STGs	Involve prescribers in the development of STGs	3.4.2
Inconsistency between the STGs and the formulary list	Review the formulary list to make it consistent with the STGs	3.2.4
Frequent drug stock-outs		
Too many drugs used, making it difficult for the pharmacy to cope	Review the formulary list to reduce the number of drugs	3.2.3, 3.2.4
Unreliable suppliers	Review the procurement system	5.3
Poor distribution	Review the distribution system	5.3
Overuse of drugs	Investigate the use of high-consumption drugs	6.2, 6.3
Insufficient budget	Review each therapeutic category in the formulary and choose the cheapest therapeutically equivalent alternative drug	3.2.3, 3.2.4, 4.3, 4.5.3
Medicines not covered by budget		
Overuse and irrational use of medicines	Investigate the use of high-consumption medicines	6.2, 6.3
Use of overly expensive medicines	Review each therapeutic category in the formulary and choose the cheapest therapeutically equivalent alternative medicine	3.2.3, 3.2.4, 4.3, 4.5.3
Medication errors reported		
Lack of staff knowledge	Educate the staff	7.2
High staff workload	Review working practices	5.2
Poor lighting and excessive noise	Arrange that dispensing procedures take place where there is good lighting and little noise	5.2
Poor communication, for example handwriting and verbal orders	Establish protocols for legible handwriting and how to write prescriptions	5.2
Complex calculation needed for prescribing	Develop or review STGs and the formulary list to simplify the calculations	3.4.1, 3.2.4
Large number of formulary medicines and dosage forms	Review the formulary list to reduce the number of medicines and dosage forms	3.2.4
Medicines reported not to work		
Inappropriate medicine use – prescribing error, medication error	Investigate the clinical use of the medicine reported not to work	5.2, 6.5, 8.1
Low medicine efficacy	Review the literature on the medicine's efficacy and its inclusion in the formulary	4.2, 4.3, 4.4

Table 9.1 *Continued*

Problem and causes	Solutions	Section
Poor medicine quality. as found by visual inspection or testing	Review the procurement process and storage. Consider changing the supplier	5.3.1, 5.3.2, 5.3.3
ADRs reported		
Inappropriate drug use – prescribing error, medication error	Investigate the clinical use of the drug reported to have caused an ADR	5.4.3, 6.5
Poor drug quality as found by visual inspection or testing	Review the procurement process and storage. Consider changing the supplier	5.3.1, 5.3.2, 5.3.3
True adverse drug reaction (ADR)	Report to the national ADR monitoring centre. Review the drug's safety profile and its inclusion in the formulary	4.3, 5.4
Overuse and irrational use of medicines		
Lack of accepted standards of use	Develop and implement STGs	3.4.1, 3.4.2
Prescriber habit	Use qualitative methods to investigate prescriber habit and then design and implement an appropriate intervention	6.4, 7.2, 7.3, 7.4, 8.1, 8.2
Prescriber lack of knowledge	Educate the prescribers using face-to-face methods as well as printed materials	7.2
Peer pressure	Identify the opinion leaders and then involve them in developing and implementing STGs and a drug use evaluation	7.2
Patient demand	Use qualitative methods to investigate patient demand and then design and implement an appropriate intervention	6.4, 7.2, 7.3, 7.4, 8.1, 8.2
Patients not getting better		
Inappropriate medicine use	Investigate the clinical use of the drugs used in patients reported to not get better	6.5, 6.3
Low medicine efficacy	Review the literature on the efficacy of drugs used in patients not getting better and inclusion of the drugs in the formulary	4.2, 4.3, 4.4
Poor medicine quality	Review the procurement process and storage of medicines used in patients not getting better. Consider changing the supplier	5.3.1, 5.3.2, 5.3.3
Wrong diagnosis	Educate the prescribers using face-to-face methods as well as printed materials	7.2
DTC not functioning		
Poor attendance at DTC meetings due lack of incentives	Discuss with senior management the possibility of giving incentives, for example time off from other duties in recognition of the DTC work, provision of food at meetings, etc.	2.2
Non-transparent decision-making leading staff to distrust the DTC	Develop and document terms of reference for the DTC, agree and document a process for managing the formulary list and making other decisions, institute the signing of conflict of interest forms by DTC members	2.1, 2.2, 3.2
Lack of belief in the need for a DTC	Provide evidence of irrational medicine use, the patient harm it causes and the financial cost	6.1, 6.2, 6.3, 6.4, 6.5

Glossary[1]

ABC analysis: Classification of inventory items into three categories (A, B and C) according to the value of their annual usage, which is used for analysing drug consumption and utilization, comparing actual versus planned purchases, justifying procurement budgets, guiding procurement patterns, and setting priorities for stock management.

ABC value analysis: Method by which medicines are divided, according to their annual usage (unit cost times annual consumption), into class A items (the 10–20% of items that account for 75–80% of the funds spent), class B items (with intermediate usage rates), and class C items (the vast majority of items with low individual usage, the total of which accounts for 5–10% of the funds spent). ABC analysis can be used to give priority to class A items in procurement, inventory control and port clearing.

Active ingredient: That portion of a medicine (drug) that has therapeutic properties.

Adherence to treatment (also **compliance**): The degree to which patients adhere to medical advice and take medicines as directed. Adherence depends not only on acceptance of information about the health threat itself but also on the practitioner's ability to persuade the patient that the treatment is worthwhile and on the patient's perception of the practitioner's credibility, empathy, interest and concern.

Basic unit: The smallest unit in which a medicine can be conveniently dispensed or administered. It is used in quantification, reorder formulas, and comparison of prices of different-sized bottles or vials. Typical basic units are tablet or capsule, mL (for liquids), and gram (for ointments and creams).

Batch: The quantity of a medicine produced in one production run.

Bioavailability: The rate and extent of availability of an active ingredient from a dosage form as measured by the concentration/time curve in the systemic circulation or its excretion in the urine.

Branded generics: Generic (off-patent) pharmaceutical products marketed under brand names.

Clinical pharmacist: An individual trained in pharmacy, usually at the bachelor's degree level, who has had specialized training in the uses, side-effects, contraindications and dosages of medications for human use.

Clinical pharmacologist: A physician who has had specialized training in the uses, side-effects, warning and dosages of medications for human use.

Co-insurance: Cost control measure in insurance schemes in which the member pays a specified percentage of the cost – for example, 25% for drugs used in serious and chronic illnesses, 50% for most other pharmaceuticals, and 75% for symptomatic treatment for minor illnesses.

Collection system: Drug distribution system in which the health facilities are responsible for providing transport of supplies from the warehouse to the health facility. Compare **delivery system**.

Community drug scheme: A form of revolving drug fund that is managed at the community level and often has broader objectives, such as health education, provision of preventive

[1] This glossary is taken from chapter 31, 'Promoting rational prescribing' in Management Sciences for Health, *Managing Drug Supply*, 2nd edn, 1997. Kumarian Press, West Hartford, CT, USA.

services, or financing of salaries, medical supplies or other costs, in addition to the financing of medicines.

Compound: To mix together the ingredients of a prescription or drug formula. Generally refers to a manual process performed for individual orders by a dispenser or pharmacist.

Consumption: The rate at which items are issued to clients or patients. This is also called demand (which is, in strict terms, the rate of requests or orders). Consumption is usually measured in terms of units consumed within a specific period.

Copayment: Cost control measure in insurance schemes in which the member pays a set charge per item received; copayment may be lower for generic drugs, higher for brand-name drugs.

Course-of-therapy prepackaging: Prepackaging of medicines in sealed plastic bags, each bag containing a complete course of treatment for that medicine, as established by standard treatment norms. The package usually contains a complete label with instructions for use.

Deductible: Payment of a specified initial amount by an insured person before services are covered; usually a set amount per quarter or per year.

Delegation: The assignment by a manager of an activity, task, defined scope of authority, or responsibility to a staff member under the manager's supervision.

Delivery system: Drug distribution system in which the warehouse is responsible for providing transport of supplies from the warehouse to the health facilities. Compare collection system.

Disintegration: The breaking up of a tablet or capsule into granules or aggregates in an aqueous fluid.

Dispense: To prepare and distribute to a patient a course of therapy on the basis of a prescription.

Dispenser: A general term for anyone who dispenses medicines. Also specifically used to mean an individual who is not a graduate pharmacist but is trained to dispense medications, maintain stock records and assist in procurement activities.

Dissolution: The breaking down of fine particles into molecules or ions homogeneously dispersed in an aqueous fluid.

Distribution system: A system of administrative procedures, transport facilities, storage facilities and user facilities through which supplies move from a central point to the user facilities.

Drug: Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. In this manual the words 'drug' and 'medicine' are used interchangeably.

Drug product: A unique combination of drugs(s), strength, and dosage form (for example, ampicillin 500 mg capsule).

Drug use: The process of diagnosis, prescribing, labelling, packaging, and dispensing and of adherence to drug treatment by patients.

Drug use evaluation: A system of ongoing, systematic, criteria-based evaluation of drug use that will help ensure that appropriate medicine use (at the individual patient level) is provided. It is the same as drug utilization review.

Efficacy: The ability of a drug to produce the purported effect, as determined by scientific methods.

Excipient: An inert substance used to give a pharmaceutical preparation a suitable form or consistency.

Exemption: A release from payment of fees for specific population groups or disease or drug types, employed in many revolving drug fund schemes to promote access to services.

Expiry date: The date appearing on a pharmaceutical product and established by the manufacturer, beyond which the manufacturer will not guarantee the potency, purity, uniformity or bioavailability of the product.

Evaluation: A periodic assessment of progress toward achieving long-term objectives and goals. Monitoring and evaluation are the third phase in the management cycle.

First-expiry/first-out procedure (FEFO): A method of inventory management in which products with the earliest expiry date are the first products issued, regardless of the order in which they are received. This method is more demanding than FIFO (see below) but should be used for short-dated products such as vaccines.

First-in/first-out procedure (FIFO): A method of inventory management in which the first products received are the first products issued. This methods generally minimizes the chance of drug expiration.

Formulary list: A list of medicines approved for use in a specific health-care setting.

Formulary manual: A manual containing clinically oriented summary pharmacological information about a selected number of medicines. The manual may also include administrative and regulatory information pertaining to medicine prescribing and dispensing.

Formulary system: The principles, criteria, procedures, and resources for developing, updating and promoting the formulary (essential medicines) list.

Generic name: The approved or nonproprietary name of a drug. It is generally the international nonproprietary name given by WHO.

Generic pharmaceutical products: Products marketed by any producer under nonpropietary or approved names.

Generic substitution: Dispensing of a product that is generically equivalent to the prescribed product, with the same active ingredients in the same dosage form, and identical in strength, concentration and route of administration.

GMP (good manufacturing practices): Performance standards for pharmaceutical manufacturers established by WHO and many national governments; they include criteria for personnel, facilities, equipment, materials, manufacturing operations, labelling, packaging, quality control and, in most cases, stability testing.

Goal: The general aim toward which the organization or programme is striving.

Health insurance: A financing scheme characterized by risk sharing in which regular payments of premiums are made by or on behalf of members (the insured). The insurer pays the cost or a set portion of the cost for covered health services.

Implementation: The second step in the management cycle; the process of putting a plan into action by organizing and directing the work. It involves managing people, money, information and other resources to achieve intended results.

Indicator: Criterion used to measure changes, directly or indirectly, and to assess the extent to which the targets and objectives of a programme or project are being attained. Indicators should meet the criteria of clarity, usefulness, measurability, reliability, validity and acceptance by key stakeholders.

Indicator drug: One of a small number of representative drugs, also known as tracer or index drugs, selected to be used with performance indicators to assess the performance of a drug supply system.

Information service: The system of records kept at offices, storage facilities and clinical facilities; forms that are used to communicate supply needs, consumption data, and other information about the system, reports that summarize that data from records and forms for planning and evaluation purposes, and procedures that coordinate the use and flow of these documents.

Inventory: The total stock kept on hand at any storage point to protect against uncertainty, permit bulk purchasing, minimize waiting time, increase transportation efficiency and buffer against seasonal fluctuations.

Inventory control: The function of supply management that aims to provide sufficient stocks of medicines at the lowest costs possible.

Irrational prescribing: Prescribing that does not conform to good standards of treatment – for example, extravagant prescribing, overprescribing, incorrect prescribing, multiple prescribing, or underprescribing of medication.

Issue unit: The quantity or size of each item counted as one inventory issue unit in the stock records. For example, in some supply systems, the unit for tetracycline capsules might be one bottle of 100 capsules; in others it might be one capsule. This is not necessarily the same as the basic unit or comparison unit, although they may be the same.

Item: A unique product for inventory purposes. In drug supply, an important issue is whether generic equivalent items are treated as the same item or whether different brands of the same generic product are treated as different items. The item is sometimes called a stock-keeping unit (SKU), which is not the same as an issue unit.

Labelling: Placing written or symbolic instruction on the immediate container in which drugs are dispensed.

Lead time: The time interval needed to complete the procurement cycle. It begins at the time the need for new stock is recognized and ends when that stock is received and available for issue.

Managed care: Insurance systems in which the insurer plays an active role in overseeing the utilization and quality of service, for example, through health maintenance organizations (HMOs), preferred provider organizations (PPOs) and managed indemnity insurance.

Management cycle: The process consisting of the three interconnected functions of planning, implementing, and monitoring and evaluation.

Medicine: Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. In this manual the words 'drug' and 'medicine' are used interchangeably.

Monitoring: The ongoing process of reviewing the degree to which programme activities are completed and objectives are being met, to allow for corrective action to be taken during implementation. Monitoring and evaluation are the third phase in the management cycle.

Multisource pharmaceutical products: Pharmaceutically equivalent products, available from different manufacturers, that may or may not be therapeutically equivalent.

Objectives: Results that a programme or workplan seeks to achieve. A well-formulated objective fits the SMART mnemonic: specific, measurable, appropriate to overall objectives or goals, realistic in terms of available resources, time-bound (there is a deadline).

Operating costs (or recurrent costs): The regular expenses of running programmes and providing services (as opposed to capital expenses).

Pharmacology: The study of medicines (drugs) and their actions.

Pharmaceutical equivalents: Products that contain the same amount of the same active substance(s) in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route.

Pharmaceutical product: A dosage form containing one or more drugs (medicines) along with other substances included during the manufacturing process.

Potency: The extent to which a medicine (drug) contains the specified amount of the active ingredient.

Prepacked kits: Also known as ration kits or set packs. An assortment of drugs and medical supplies to cover a set number of patient attendances, which are distributed unopened to health facilities.

Prescribing: The act of determining what medication the patient should have and the correct dosage and duration of treatment.

Private health insurance: Voluntary private indemnity insurance provided by private insurance companies through employees, mutual societies or cooperatives.

Procurement: The process of acquiring supplies, including those obtained by purchase, donation and manufacture.

Pull system: Drug distribution system in which each peripheral facility determines the drug quantities to be requisitioned from the procurement unit or warehouse. Compare **push system**.

Push system: Drug distribution system in which the procurement unit or warehouse determines what drug quantities are to be issued to the peripheral facilities. Compare **pull system**.

Purity: The extent to which drugs are free from potentially harmful contaminants, significant quantities of other drugs, bacteria or other microorganisms.

Quality assurance: The management activities required to ensure that the drug that reaches the patient is safe, effective, and acceptable to the patient.

Quality control: The testing of drug samples against specific standards of quality.

Revolving drug funds: A drug sales programme in which revenues from drug fees are used to replenish drug supplies.

Shelf-life: The length of time a material may be stored without affecting its usability, safety, purity or potency.

Social health insurance: Compulsory health insurance provided to civil servants, people in the formal employment sector, and certain other groups through programmes such as social security funds, national health insurance funds, and other systems. Premiums are often deducted directly from salaries or wages.

Specifications: A precise description of an item to be procured, including any special requirements.

Standard treatment guidelines: Agreed-upon treatment practices for a diagnosed illness; may include more than details of drug treatment.

Stock: Goods and materials stored for future use.

Stock records: A generic term that applies to card record systems, stock ledgers and computer files. These provide basic information for inventory management by recording all transactions for an item, including receipts, issues, orders placed, orders received and stock losses.

Stockout: Complete absence of an item that is normally expected to be on hand. In many cases, this can be misleading as an indicator, because a warehouse may always reserve a small stock – the warehouse is not literally out of stock, but there is a functional stockout because the warehouse will not issue the reserved stock.

Strategy: A broad plan of action for fulfilling a programme's basic purpose and achieving its main goals.

Supervise: To oversee; to provide direction; to guide and instruct with immediate responsibility for performance.

Supplier: Any individual or company that agrees to provide medications, regardless of whether that party is the manufacturer.

Symbolic labelling: A system of providing written instructions for patients using sketches and other graphic representations.

Targets: Measurable, time-limited, intermediate progress points toward objectives; also called milestones.

Therapeutic category analysis: The analysis of expenditures by therapeutic category, for comparison with morbidity patterns and public health priorities, as a means of focusing cost control efforts.

Therapeutic equivalents: Pharmaceutically equivalent products whose effects with respect to both safety and efficacy are essentially the same, when administered in the same

molar dose, as can be derived from appropriate studies (bioequivalence, pharmacodynamic, clinical, or in-vitro studies).

Therapeutic substitution: Interchange of one pharmaceutical product with another that differs in composition but is considered to have similar pharmacologic and therapeutic activities in accordance with written protocols previously established and approved.

Users fees: Charges paid by the users of a service.

VEN system: A system of setting priorities for purchasing drugs and keeping stock, in which drugs are divided according to their health impact into vital, essential, and non-essential categories.

Waiver: A release from payment of fees based on financial hardship, employed in many revolving drug fund schemes to promote access to services.

Wholesaler: A dealer who purchases supplies from a manufacturer and resells them to the ultimate buyers.

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American Society for Microbiology, 1325 Massachussets Ave, N.W. Washington DC 20005, USA.

Biomed: http://www.agreecollaboration.org

Essential Drugs Programme South Africa, National Department of Health, the Directorate: Pharmaceutical Programs and Planning, Private Bag X828, Pretoria 0001, South Africa; websites: http://www.doh.gov.za; http://pharmis.pwv.gov.za/publications1.htm

Kumarian Press Inc., 14 Oakwood Ave., West Hartford, CT 06119-227, USA; http://www.kpbooks.com

Management Sciences for Health, 165 Allandale Road, Boston, MA 02130-3400, USA. Tel. +1 617 524 7799; Fax: +1 617 524 2825; email: bookstore@msh.org; websites: http://www.msh.org/resources/publications/index.html and http://erc.msh.org

Programme for Appropriate Technologies in Health (PATH), 4 Nickerson St., Seattle, WA 98109-1699, USA; website: http://www.path.org/resources/safe-inj-pdf.htm

Safe Injection Global Network, secretariat at WHO Geneva; website: http://www.injectionsafety.org

Scottish Intercollegiate Guidelines Network (SIGN), 9 Queen Street, Edinburgh EH2 1JQ, Scotland, UK; website: http://www.sign.ac.uk

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WHO Essential Drugs and Medicines Policy Department, CH 1211 Geneva 27; website: http://www.who.int/medicines

WHO Drug Price Information Services; website: http://www.who.int/medicines/organization/par/ipc/drugpriceinfo.shtml

WHO Publications, Geneva; email: bookorders@who.int; website: http://www.who.int/pub/en

Index

Abbreviations used in the index: ADR, adverse drug reaction; DTC, drug and therapeutics committee; DUE, drug use evaluation; STGs, standard treatment guidelines; VEN, vital, essential and non-essential analysis.

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