Drug and Therapeutics Committee
Training Course

Participant’s Guide
All Sessions
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RPM Plus works in more than 20 developing and transitional countries to provide technical assistance to strengthen pharmaceutical and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning, and in promoting the appropriate use of health commodities in the public and private sectors.

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ABBREVIATIONS AND ACRONYMS

A+L    artemesunate plus lumefantrine
A+M    artemesunate plus mefloquine
AB     antibiotic
ACS    acute coronary syndrome
ACT    artemisatin-based combination therapy
ADR    adverse drug reaction
AIDS   acquired immunodeficiency syndrome
AMR    antimicrobial resistance
AOF    antibiotic order form
ARI    acute respiratory infection
AUD    Australia, dollars
BCG    bacillus Calmette-Guérin
bid    twice a day (bis in die)
CI     confidence interval
CD4    human T helper cells expressing CD4 antigen (T helper cell)
CEA    cost-effectiveness analysis
CER    cost-effectiveness ratio
CMA    cost-minimization analysis
CrCl   creatinine clearance
CUA    cost-utility analysis
DALY   disability-adjusted life year
COA    certificate of analysis
DOB    date of birth
DPT    diphtheria, pertussis, tetanus
DDD    defined daily dose
DTC    Drug and Therapeutics Committee
DUE    drug use evaluation
DUR    drug use review (per CPM word list)
EDP    essential drugs program
EML    essential medicines list
FGD    focus group discussion
g      gram
GI     gastrointestinal
GMP    Good Manufacturing Practices
h      hour
HbA1c  glycosylated hemoglobin
HIV    human immunodeficiency virus
HMO    health maintenance organization
HR     hazard ratio
IC     infection control
ICAT   Infection Control Assessment Tool
ICC    Infection Control Committee
ICER   incremental cost-effectiveness ratio
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>ITT</td>
<td>intention to treat</td>
</tr>
<tr>
<td>INN</td>
<td>international nonproprietary name</td>
</tr>
<tr>
<td>INRUD</td>
<td>International Network for Rational Use of Drugs</td>
</tr>
<tr>
<td>iv or IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>mcg</td>
<td>microgram</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>ml</td>
<td>milliliter</td>
</tr>
<tr>
<td>MRSA</td>
<td>methicillin-resistant staphylococcus aureus</td>
</tr>
<tr>
<td>MSH</td>
<td>Management Sciences for Health</td>
</tr>
<tr>
<td>MUR</td>
<td>medicine use review</td>
</tr>
<tr>
<td>n or N</td>
<td>number</td>
</tr>
<tr>
<td>ng</td>
<td>nanogram</td>
</tr>
<tr>
<td>NDA</td>
<td>national drug authority</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>ORS</td>
<td>oral rehydration salts (used without being defined in slides)</td>
</tr>
<tr>
<td>PHC</td>
<td>public health care</td>
</tr>
<tr>
<td>po</td>
<td>per os (by mouth)</td>
</tr>
<tr>
<td>PTC</td>
<td>Pharmacy and Therapeutics Committee</td>
</tr>
<tr>
<td>q</td>
<td>quart</td>
</tr>
<tr>
<td>QI</td>
<td>quality improvement</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
</tr>
<tr>
<td>RCQI</td>
<td>rapid cycle quality improvement</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RPM Plus</td>
<td>Rational Pharmaceutical Management Plus [Program]</td>
</tr>
<tr>
<td>RRR</td>
<td>relative risk reduction</td>
</tr>
<tr>
<td>SK</td>
<td>streptokinase</td>
</tr>
<tr>
<td>STG</td>
<td>standard treatment guideline</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>tid</td>
<td>three times a day (ter in die)</td>
</tr>
<tr>
<td>TOR</td>
<td>terms of reference</td>
</tr>
<tr>
<td>TOT</td>
<td>training of trainers</td>
</tr>
<tr>
<td>tPA</td>
<td>tissue plasminogen activator</td>
</tr>
<tr>
<td>UC</td>
<td>usual care</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>UNIPAC</td>
<td>UNICEF Supply Division Warehouse Procurement and Assembly Center</td>
</tr>
<tr>
<td>URTI</td>
<td>upper respiratory tract infection</td>
</tr>
<tr>
<td>USD</td>
<td>U.S. dollar</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>VA</td>
<td>visual aid</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>VEN</td>
<td>vital, essential, nonessential</td>
</tr>
<tr>
<td>VRE</td>
<td>vancomycin-resistant enterococcus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant tuberculosis</td>
</tr>
</tbody>
</table>
Drug and Therapeutics Committee
Training Course

Session 1.
Drug and Therapeutics Committee—Overview
SESSION 1. DRUG AND THERAPEUTICS COMMITTEE—OVERVIEW

Purpose and Content

The Drug and Therapeutics Committee (DTC) is an essential component of a health care organization’s medicine selection, use, and distribution program. This committee has many different functions that will contribute to the goal of improving medicine selection and rational use of medicines. This session provides an overview of the role and functions of a DTC and describes all aspects of this important committee.

This training series is intended for practitioners who serve on a DTC. The emphasis of this session and of the entire training series is on the technical aspects of a DTC, including medicine selection for the formulary, identification of medicine use problems, and the promotion of interventions to improve medicine use. Participants are referred to the “Further Readings” section for information on the establishment and implementation of a new DTC. The WHO publication Drug and Therapeutics Committee: A Practical Guide provides step-by-step procedures for starting a new DTC.

Objectives

After attending this session, participants will be able to—

- Understand the role of the DTC
- Understand DTC structure and organization and its relationship to other hospital committees
- Understand the functions of a DTC, including advisory responsibilities, development of policies and procedures, formulary management, identification of medicine use problems, and promotion of strategies to improve medicine use and medicine safety.
- Discuss the importance of the DTC in promoting rational use of medicines, especially antimicrobial use and injections

Preparation and Materials

- Read the Participants’ Guide
- Read the World Health Organization (WHO) manual Drug and Therapeutics Committees: a Practical Guide. (See “Further Readings” below.)
Further Readings


Introduction

Key Definitions

Drug and Therapeutics Committee (DTC)—The committee that evaluates the clinical use of medicines, develops policies for managing pharmaceutical use and administration, and manages the formulary system.

Formulary Committee—The committee dedicated to selecting, developing, and maintaining a list of approved medicines for the hospital or clinic.

Formulary—A list of medicines that are approved for use in the health care system by authorized prescribers.

Formulary System—A system of periodically evaluating and selecting medicines for the formulary, maintaining the formulary, and providing information in a suitable manual or list.

Medicine Use Problems and the Need for a DTC

Many countries will spend 30 to 40 percent of their health care budgets on pharmaceuticals, and much of that money is wasted because of irrational use and inefficiencies in procuring medicines. Other serious problems that health care organizations face include the overuse of antibiotics, increasing antimicrobial resistance, increasing adverse drug reactions (ADRs), and considerably higher costs associated with pharmaceutical use. DTCs can provide the leadership and structure to select appropriate medicines for the formulary, identify medicine use problems, promote rational use of medicines, and help reduce pharmaceutical costs.

Many surveys worldwide have revealed inappropriate medicine use. Examples are taken mainly from Quick and others (1997), Managing Drug Supply, the 2004 international conference on improving the use of medicines, the website http://www.icium.org, and the WHO Database on Drug Use in Primary Health Care in Developing Countries, 2001–2006. Results from the latter database can be accessed from the WHO medicines website under—

- Presentations given at the Technical Briefing Seminar, which is conducted by WHO Geneva every year and can be accessed at http://www.who.int/medicines/areas/policy/en/index.html
- Briefing given to delegates at the 60th World Health Assembly in 2007, which can be accessed at http://www.who.int/medicines/areas/rational_use/WHA60NGObriefingshortMay07.pdf.

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The sources show that—

- 30–60 percent of primary health care patients receive antibiotics, perhaps twice what is clinically needed. 2

- 6–90 percent of patients receive inappropriate antibiotics in teaching hospitals (adapted from Hogerzeil 1995, pp.1–6).

- Standardized surveillance of outpatient use of antibiotics in Europe showed that in 2002, France consumed three times as more antibiotics than the Netherlands even though these countries are neighbors and are likely to have the same case-mix (Goosens et al. 2005). Surveillance of antimicrobial resistance in Europe and some other countries has shown that resistance of \textit{S. pneumonia} to penicillin is correlated with use; that is, countries using more antibiotic had more resistance (Albrich, Monnet, and Harbath 2004).

- Overall in developing countries at primary health care level, less than 70 percent of pneumonia cases are treated with an appropriate antibiotic, and yet more than half of all viral upper respiratory tract infections are treated inappropriately with antibiotics; furthermore, doctors, paramedical workers, and nurses all seemed to perform equally (WHO/PSM Database on Medicines Use in Primary Health Care in Developing Countries, 2007).

- Overall in developing countries at primary health care level for the treatment of acute diarrhea, less than half are treated appropriately with oral rehydration solution, and yet about half are treated with antimicrobials, which is rarely necessary; furthermore, treatment in the private sector was considerably poorer than in the public sector (WHO/PSM Database on Medicines Use in Primary Health Care in Developing Countries, 2007).

- About half of all patients at the primary health care level in developing countries in all regions are not treated in compliance with clinical guidelines (WHO/PSM Database on Medicines Use in Primary Health Care in Developing Countries, 2007).

- 5–50 percent of primary health care patients receive injections, up to 90 percent being medically unnecessary. Many of these injections are not given in a sterile manner, and so cause the spread of bloodborne infections such as hepatitis B and C and HIV/AIDS (adapted from (1) Managing Drug Supply 1997; (2) Simonsen 1999; (3) Hutin 2003).

A health care organization’s DTC has numerous responsibilities that, when performed successfully, will have a positive impact on health care. The overall value of the DTC is not

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easily measured, but many authorities agree that it is a valuable component of a comprehensive health care system. Some of the important benefits of a functioning DTC are—

- Selection of effective, safe, high-quality, and cost-effective pharmaceuticals for the formulary
- Identification of medicine use problems that can lead to improved medicine use, including antimicrobial use
- Improved medicine use, including antimicrobial use
- Improved quality of patient care and health outcomes
- Management of antimicrobial resistance
- Increased staff and patient knowledge
- Decreased ADRs and medication errors with improved management
- Improved medicine procurement and inventory management
- Management and control of pharmaceutical expenditures through better management

Role and Functions of a DTC

The DTC’s role is to optimize rational use of medicines by evaluating the clinical use of pharmaceuticals, developing the policies for managing medicine use and administration, and managing the formulary system. The committee has broad responsibilities in determining what medicines will be available, at what cost, and how they will be used.

The committee’s functions are numerous and may be only partially performed by other committees. The primary functions are—

- Advising medical, administrative, and pharmacy departments on pharmaceutical related issues
- Developing pharmaceutical policies and procedures
- Evaluating and selecting medicines for the formulary and providing for its periodic revision
- Identifying medicine use problems
• Promoting and conducting effective interventions to improve medicine use (including educational, managerial, and regulatory methods)

• Managing ADRs and medication errors

**Advising Medical Staff, Administration, and Pharmacy**

The DTC is a valuable asset to the medical staff, administration, pharmacy, and other departments within the health care organization. The committee provides advisory services to these departments on all aspects of pharmaceutical selection, use, and distribution. Typically, the DTC provides recommendations and advice, whereas the executive or medical staff committee takes action on these recommendations and implements approved decisions.

Many other departments and medical services, including the nursing department, public health, the Infection Control Committee, immunization programs, and dental services, would benefit from the DTC and its advisory services in both public and private sectors.

**Developing Drug Policies and Procedures**

The DTC is responsible for developing pharmaceutical policies in the health care organization. These policies are necessary to adequately control important aspects of medicine selection, purchase, distribution, use, and administration. The DTC is the logical choice for performing these tasks, since its members have the most experience and training in pharmaceutical therapy and distribution. Policies and procedures are generally the first order of business in the committee, because they will provide the foundation for other functions that evolve from the committee. Besides general policies about medicine use, the following specific policies should be in place—

• Addition of new medicines
• Nonformulary medicines
• Restricted medicines
• Investigational medicines
• Standard treatment guidelines (STGs) and other interventions to improve medicine use
• Generic substitution and therapeutic interchange
• Automatic stop orders
• Structured order forms and guidelines
• Pharmaceutical representatives and promotional literature

The development of comprehensive policies and procedures is critical to the success of the DTC. These policies will provide the framework for implementing improvements in medicine selection and use.
**Evaluating and Selecting Medicines for the Formulary**

One of the most important functions of the DTC is the evaluation and selection of medicines for the health care organization’s formulary. Evaluating medicines and consequently approving or rejecting them requires significant expertise and commitment from the committee.

The evaluation of medicines will require a rigorous approach that looks at documented efficacy, safety, quality, and cost of all medicines requested for the formulary. A system of periodic review of medicines on the formulary is also needed because the information base about medicines is constantly changing. These changes may be reflected in new indications, information about efficacy and safety, and comparative information with other medicines. The cost of a medicine, whether it is a new medicine or a generic that has been on the formulary for many years, may change frequently and requires frequent evaluation. Consistent decision making is necessary in the selection of medicines and involves—

- Evidenced-based medicine
- Consideration of local context
- A transparent evaluation process

Evaluating medicines for the formulary includes the review of generic medicines and other therapeutic equivalents so the most cost-effective formulary for the hospital and primary care clinic can be established. The evaluation process should include review of the primary pharmaceutical literature (especially randomized controlled trials), published STGs, pharmacoeconomic studies, review articles, and reliable textbooks.

**Identifying Medicine Use Problems**

The DTC is required to assess the quality of care (related to medicine use) in a consistent, ongoing fashion. This responsibility, however, is frequently overlooked. Time and attention here will have significant return in the long term with improved quality of pharmaceutical therapy, improved patient outcomes, and decreased pharmaceutical costs. Several pharmaceutical management areas need to be assessed to identify medicine use problems—

- Pharmaceutical procurement and availability
- Pharmaceutical distribution
- Medicine prescribing
- Dispensing
- Administration and use
- ADR reports
- Medication error reports
- Antimicrobial resistance surveillance reports

Many different methods are used to assess the quality of care, including the following that will be discussed in this training series: ABC and vital, essential, nonessential (VEN) analyses, defined daily dose (DDD) analysis, aggregate data analysis, health care facility indicators, hospital antimicrobial indicators, and drug use evaluation (DUE or drug use review).
Promoting Interventions to Improve Medicine Use

Irrational use of medicines, a common problem present in all health care systems worldwide, contributes to poor patient outcomes and wastes valuable resources. Promoting and implementing effective interventions are necessary to ensure rational use of medicines. Important interventions to improve medicine use are as follows—

- Educational programs
  - Drug bulletins and newsletters
  - In-service education

- Managerial programs
  - Development of STGs
  - DUE
  - Clinical pharmacy programs
  - Structured order forms and automatic stop orders

- Regulatory programs
  - Pharmaceutical registration
  - Professional licensing
  - Pharmaceutical outlet licensing

Managing Adverse Drug Reactions

The committee must address the issue of ADRs to medications on a regular basis. ADRs are a serious problem with increasing incidence, as more medicines become available and more people become exposed to them. In the United States, a review of prospective studies showed that in 1994, hospitalized patients had 2.2 million ADRs (6.7 percent incidence) and an estimated 106,000 fatalities. Other studies have shown that ADRs account for 3–7 percent of all hospital admissions. These data become more significant when you consider that the statistics in these studies do not include errors of administration, which would only increase the total incidence of morbidity and mortality. The DTC should have a plan to address the problems of ADRs including regular monitoring, assessment, reporting, correcting identified problems, and prevention.

Newly released medicines can be a problem because of lack of knowledge and inadequate clinical experience associated with them. The current trend to “fast track” pharmaceuticals into distribution is also increasing the incidence of adverse side effects because these new medicines may not have been adequately tested before release by regulating authorities. Older medicines may produce just as many side effects, but their effects are largely known and can be anticipated and prevented in many instances.

Managing Medication Errors

Medication errors may occur in prescribing a medicine, in preparing and dispensing by a pharmacist, in preparing and administering by a nurse, and when a patient takes the medicine. The problem is pervasive and occurs with all persons who handle medications. The causes of errors are numerous and include lack of knowledge, fatigued employees, careless work attitudes, poor procedures for pharmaceutical distribution, and mental mistakes. Errors will occur no matter how ideal a health care setting may be. Therefore, the DTC must provide the mechanism to monitor, assess, and prevent medication errors.

Organization of a DTC

The DTC is usually made up of health care professionals from the medical staff (with representatives of the major specialties), pharmacists, nursing personnel, and representatives from administration. Although this mix of personnel would provide the most input from diverse segments of the health care organization, no single recommendation that dictates who is on this committee. Since to a large extent the committee regulates what physicians will be prescribing and how pharmacists are involved with pharmaceutical therapy and logistics, these professionals will need a significant voice on the committee.

Ideally, a well-known and respected physician will provide leadership for the committee, with a pharmacist as co-chair or executive secretary. These individuals should be appointed by the health care organization’s administration. The committee must maintain a line of authority and support to top management in the health care system. Figure 1 illustrates a DTC’s typical organization.

When specific medicines are being considered, the committee may invite specialists to participate in meetings as needed; these individuals do not have voting privileges. Subcommittees may be formed to carry out specific tasks, for example, therapeutic class review of antimicrobial medicines or the development of a medication error prevention strategy.

Meeting regularly, at least three to six times a year, is very important for the DTC. If necessary, the committee will need to enforce mandatory attendance to accomplish the functions of the committee. Minutes are prepared for each meeting and distributed to appropriate medical, nursing, and pharmacy departments.

Finally, all goals, terms of reference, policies, decisions, and other actions of the DTC should be documented and the records should be kept.
Figure 1. Drug and Therapeutics Committee Organization Chart

**Antimicrobial Subcommittee**

Many DTCs have found it necessary to form an associated subcommittee of the DTC that deals solely with antimicrobials. The purpose and goal of this subcommittee is to ensure that safe, effective, cost-effective antimicrobials are made available to the health care organization. This subcommittee also dedicates itself to ensuring that antibiotics are used only when clinically indicated, at the correct doses, and for the appropriate duration of time. The subcommittee must also ensure that patients are taking these medicines correctly, because correct use may have a profound effect on treatment outcomes and the prevention of antimicrobial resistance.

Functions of the antimicrobial subcommittee are similar to the DTC, but with an emphasis on antimicrobial medicines. Ideally, an antimicrobial subcommittee would function as follows—

- Address issues relating to antimicrobials including correct prescribing
- 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
- Assist in evaluating and selecting antimicrobials for the formulary
- Organize educational programs for health care staff
- Assess and monitor antimicrobial sensitivities and resistance patterns in hospitals and primary care clinics; prepare monthly reports of these activities and disseminate to appropriate departments and health care professionals
Infection Control Committee

The Infection Control Committee oversees the hospital’s infection control, prevention, and monitoring programs. This committee operates independently of the DTC, but frequently relies on the DTC’s advisory function. Infection Control Committees perform the following major functions—

- Develop and recommend policies and procedures pertaining to infection control
- Address food handling, laundry handling, cleaning procedures, visitation policies, and direct patient care practices, including hand washing and immunizations
- Obtain and manage critical bacteriological data and information, including surveillance data
- Recognize and investigate outbreaks of infections in the hospital and community
- Educate and train health care workers, patients, and nonmedical caregivers

Figure 2 illustrates the organizational structure of these committees within the health care organization.
**Guiding Principles for DTCs**

For a DTC to be effective, certain principles must be adopted and followed throughout the committee activities and proceedings. These principles can be applied to any committee or any function of the health care system.

- **Transparent and unbiased decision-making**
  - Explicit criteria and process
  - Documentation of activities
  - Absence of conflict of interest including pharmaceutical manufacturers and suppliers
  - Development and enforcement of a strict ethics policy for all committee activities

- **Objectivity**—Evidence-based approach and levels of evidence

- **Consistency**—Activities of the committee are consistent and follow established policies and procedures. Medicines in the formulary and STGs consistent throughout the health care system.

- **Impact orientation**—Indicators of process, impact, and outcome show improved health care results.
Factors Critical for Success of a New or Long-Standing DTC

- Establish clear goals and purpose
- Obtain wide representation on the committee—prescribers, nurses, pharmacists, administration
- Permit no relationship of the committee or committee members with pharmaceutical manufacturers or suppliers
- Communicate all DTC information, policies, procedures, recommendation, and actions to staff
- Obtain official status approved by the administration (local hospital director and regional health bureaus) with strong management support—important issue
- Ensure the committee has a motivated, respected, and dynamic chairperson and members
- Develop support from medical and pharmacy departments and local professional schools
- Ensure contextual incentives

Ethical Concerns of the DTC

The committee needs to operate in a manner that ensures transparency and avoids conflicts of interest with manufacturers and distributors of pharmaceuticals and medical supplies. For the committee to maintain objectivity and credibility, a strict ethics policy must be developed and rigorously enforced at all times. The committee can have no relationship with pharmaceutical companies other than a purely professional one that encourages the acquisition of quality medicines and the flow of unbiased information about their products.

Monitoring DTC Performance

DTCs are present in many hospitals and clinics, but many are not effective in improving the use of medicines or in managing pharmaceutical distribution. The following process and outcome indicators will help identify when a DTC is effective and making an impact.

Process indicators—

- Is there a DTC document that indicates terms of reference (TOR) including goals, objectives, functions, and membership?
- Is a budget allotted to DTC functions?
- What percentage of DTC members attend more than half of meetings?
- How many DTC meetings are held per year?
• Are there documented criteria for addition and deletion of medicines to the formulary?
• Have STGs been developed, adapted, adopted, and implemented?
• How many education programs were presented in the last year?
• How many intervention studies to improve medicine use have been conducted?
• How many DUEs have been undertaken?
• Is there any documented policy for controlling access of pharmaceutical manufacturing representatives and promotion literature to hospital staff?

Outcome indicators—

• Medicine selection
  o Number of medicines on the hospital formulary
  o Percentage of prescribed medicines on the formulary
  o Number of antimicrobials on the formulary

• Prescribing quality
  o Percentage of patients treated in accordance with STGs
  o Percentage of pharmaceutical treatments meeting agreed criteria of DUE

• Pharmaceutical safety—Mortality and morbidity rated per annum due to adverse consequences of medicine use (ADRs and medication errors)

• Financial sustainability—Cost of DTC activities versus the money saved through improving pharmaceutical use and decreasing waste

Activity

Review of the Participants’ DTC

To start our activities for this DTC training program, it would be helpful to review the kinds of programs that your DTC provides. Please take a few minutes and answer the following questions using the Drug and Therapeutics Committee Questionnaire (annex 1). Please tear the completed form from your Participant’s Guide and hand it in to the session moderator.

During this activity, participants will be asked to discuss individual challenges and barriers to starting and maintaining a DTC. This discussion is important because it will give all of the participants and the trainers knowledge of the existing challenges and barriers and will help guide the training to identify solutions to some of these issues.
Summary

The Drug and Therapeutics Committee should be a dynamic, integrated, and productive organization that deals with all issues concerning the use of medicines. The committee can provide leadership in promoting rational use of medicines.

Important functions of the committee include—

- Advising medical, administrative, and pharmacy departments
- Developing policies and procedures for the use and distribution of medicines
- Evaluating and selecting medicines for the formulary and providing for its constant revision
- Identifying medicine use problems
- Promoting effective interventions to improve medicine use including educational, managerial, and regulatory activities
- Managing ADRs and medication errors

Factors critical for success include the following—

- Clear goals and purpose
- Wide representation—prescribers, nurses, pharmacists, administration
- No relationships between DTC and manufacturers or suppliers
- Communications to staff of all DTC information, policies, procedures, recommendation, and actions
- Official status approved by administration (local and Ministry of Health) with strong management support
- Motivated, respected, and dynamic chairperson
- Promotion and support by medical and pharmacy departments and local professional schools
- Contextual incentives
Annex 1. Drug and Therapeutics Committee Questionnaire

Name ________________________________________________________________

Town/city ______________________________________________________________

Name of work site _______________________________________________________

Region _________________________________________________________________

Please completely fill out the questionnaire below. If your health care facility does not have a DTC, please indicate whether the activity mentioned in the question is done by another organization within your health care facility.

<table>
<thead>
<tr>
<th>DTC Question</th>
<th>Answer</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Does your hospital have a DTC?</td>
<td>Yes</td>
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<tr>
<td>If yes, how many years has the DTC been established?</td>
<td>No</td>
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<td>Number of years _____________</td>
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<td>Does your DTC have a Subcommittee on Antimicrobials?</td>
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<td>Does your hospital have an Infection Control Committee?</td>
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<td>What are the major functions of your DTC?</td>
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<td>DTC Question</td>
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<tr>
<td>Does your DTC have guidelines and procedures that regulate the functions of the DTC?</td>
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<td>What professional staff members are represented on the committee? Please list them</td>
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<td>How many members typically attend DTC meetings? Please list those who usually attend</td>
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<td>Who serves as the DTC chairperson?</td>
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<td>Who serves as the secretary?</td>
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<td>How often does the DTC meet?</td>
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<td>What topics are covered in the regular meetings of the DTC?</td>
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<td>Do you maintain minutes of the DTC meeting?</td>
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<td>Does your hospital have a medicine formulary?</td>
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<tr>
<td>Does your committee routinely evaluate new requests for the formulary or essential medicines lists?</td>
<td>Yes _____</td>
<td>No _____</td>
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<tr>
<td>Does your committee regularly review the formulary for availability of the most effective, safe, and cost-effective medicines?</td>
<td>Yes _____</td>
<td>No _____</td>
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<tr>
<td>How many chemical entities are in your formulary?</td>
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<td>How many medicine products (including different formulations and different banded products of the same chemical entity)?</td>
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<td>Approximately how often do prescribers prescribe medicines that are not in the formulary list?</td>
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<td>Is there a medicine information center in your hospital?</td>
<td>Yes _____</td>
<td>No _____</td>
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<td>If no, does your hospital have plans to institute one?</td>
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<td>DTC Question</td>
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<td>Comments</td>
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<td>What sources of pharmaceutical information are used to evaluate medicines for the formulary? (Please list each source.)</td>
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<td>Does your DTC have an Internet connection for pharmaceutical information searches?</td>
<td>Yes ____</td>
<td>No ____</td>
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<tr>
<td>Who provided the medicine information sources for your hospital and when did this occur?</td>
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<td>What is the role of pharmaceutical companies or suppliers in providing information on new medicines and promoting medicines in your institution?</td>
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<tr>
<td>Does your DTC have established policy for evaluating adverse drug reactions?</td>
<td>Yes ____</td>
<td>No ____</td>
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<tr>
<td>Does your DTC have established policies to assure product quality?</td>
<td>Yes ____</td>
<td>No ____</td>
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<td>DTC Question</td>
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<tr>
<td>Does your DTC participate in evaluating pharmaceutical costs?</td>
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<td>Does your DTC have established methods for periodically evaluating the use of medicines in the hospital? If yes, what methods are used?</td>
<td>Yes __________</td>
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<td>No __________</td>
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<td>Has the committee detected any problems in the use of medicines? If yes, please describe the problems.</td>
<td>Yes __________</td>
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<td></td>
<td>No __________</td>
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<td>Does your DTC have programs or strategies to improve pharmaceutical use problems? What are these strategies?</td>
<td>Yes __________</td>
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<td>No __________</td>
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<tr>
<td>Does your DTC participate in preparing technical specifications for procurement of medicines?</td>
<td>Yes __________</td>
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<td>What are some major accomplishments of the committee?</td>
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<td>DTC Question</td>
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<tr>
<td>What are major problems of your committee?</td>
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<td>What would you like to see accomplished with your committee?</td>
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Session 2.
Developing and Maintaining a Formulary
SESSION 2. DEVELOPING AND MAINTAINING A FORMULARY

Purpose and Content

Session 2 provides information about the formulary system and how it functions within the Drug and Therapeutics Committee (DTC). There will be discussion about implementing and maintaining a formulary, a description of criteria for evaluating medicines for the formulary, and a review of pharmaceutical information resources.

As many as 50 percent of all medicines on the market today are either duplicative or of questionable value, so the health care system is forced to institute its own complex screening methods to provide the most efficacious, safe, and cost-effective medicines. The problem of an over-selection of medicines will only increase as more medicines are produced by manufacturers and distributors in search of greater profits.

Benefits arising from the appropriate selection of medicines are numerous and include improved drug therapy, decreased adverse drug reactions (ADRs), improved efficiency in procurement and inventory management, and decreased overall health care cost.

Objectives

After attending this session, participants will be able to—

- Define the formulary system concept
- Understand basic formulary management principles
- Describe the benefits of an effective formulary system
- Identify criteria used for selection of medicines
- Describe basic pharmaceutical information resources for evaluating medicines

Preparation and Materials

Read—

- Participants’ Guide
- Managing Drug Supply, Chapter 10, “Managing Drug Selection”
- Managing Drug Supply, Chapter 11, “Treatment Guidelines and Formulary Manuals”

Further Readings


Key Definitions

**Formulary**—A list of medicines approved for use in the health care system by authorized prescribers

**Formulary manual**—The document that describes medicines that are available for use in the hospital and clinics (provides information on indications, dosage, length of treatment, interactions, precautions, and contraindications)

**Formulary system**—The system of periodically evaluating and selecting medicines for the formulary, maintaining the formulary, and providing information in a suitable manual or list

Introduction

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence and 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.⁶

Formularies or essential medicines and formulary systems are the backbone of the DTC. The formulary provides many benefits in providing improved patient care at decreased cost through improved selection and rational medicine use. The formulary system also improves efficiency within the procurement and inventory management programs.

A comprehensive and active formulary system provides numerous benefits to hospitals and primary care clinics, including the following—

- Approved and efficacious medicines that all practitioners will be required to use.
  - Only the most effective and safest products will be available.
  - Available medicines will have been evaluated in a systematic manner.
  - Medicines will be chosen and approved to treat the disease states of the region or country.

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Physicians will develop better experience with fewer medicines. Training will be easier because there will be fewer medicines on which to concentrate teaching activities.

- Drug therapy at a lower overall cost
  - Ineffective, high-cost medicines will not be available.
  - The most effective medicines will be available to treat common health problems, resulting in fewer visits, improved outcomes, and subsequently lower costs.
  - Inventory cost will be reduced.

- Consistent supply of medicines
  - Managing and regulating the number of medicines and improving the procurement and inventory management systems will lead to fewer medicines being ordered in larger quantities.
  - These actions will enhance price competition and economies of scale with regard to quality assurance, procurement, storage, distribution, and dispensing, and will subsequently lead to improved availability of medicines.
  - Less money will be wasted, making it possible to be more consistent in purchasing essential medicines and increasing availability.

The DTC and formulary system drive the entire health care system in the direction of improved patient outcomes at reduced costs. Every step in the formulary system will result in a more efficient system that will better utilize scarce health care resources.

**Formulary Management Principles**

The formulary is a periodically revised list of medicines that reflects the current judgment of the medical staff. The formulary system utilizes the medical and pharmacy staff to evaluate, appraise, and select from among the numerous available medicines those products that are the most efficacious, safest, of adequate quality, and available at a reasonable price. When completed, the formulary should conform to the following principles—

- Medicines should be selected based on the needs of the community; they should treat the locally identified diseases and conditions.
- Medicines selected for the formulary are “medicines of choice.”
• The formulary list should have a limited number of medicines, only those necessary to provide for the needs of the hospital or clinic; duplication of agents that have therapeutic equivalence should not occur.

• International nonproprietary names (INN) (i.e., generic names) should be used.

• Combination (fixed-dose) products should be used only in specific proven conditions (e.g., to treat tuberculosis).

• Medicines need to be selected based on explicit criteria that include proven efficacy, safety, quality, and cost.

• The formulary must be consistent with any national or regional formulary or approved standard treatment guidelines.

• Medicines should be restricted to appropriate practitioners.

Maintaining a Formulary System

The formulary maintenance process is dependent on two key components: (a) additions and deletions of medicines, and (b) therapeutic medicine class reviews. Additions and deletions should be handled following specific policies and procedures developed for the DTC. A transparent methodology must be developed for these important decisions concerning addition or deletion of a medicine. See the next section (“Process for Selecting New Medicines”) for recommended criteria for adding medicines to the formulary.

Routine medicine class reviews are important to maintain the formulary. The medicine class review involves the evaluation of a complete section of medicines (e.g., cephalosporin antibiotics). This review would evaluate current medicines on the formulary in a systematic manner so that the entire formulary is reviewed over a two- to three-year period. This task is difficult, but it will provide the necessary review and analysis of formulary medicines that is so important in a medical discipline that is changing rapidly. Any new medicines that would offer an advantage over the current selections would be evaluated and considered for the formulary. Medicines that are no longer used or lack sufficient evidence of efficacy, safety, and quality should be recommended for deletion. Medicines that no longer meet the criteria for being cost-effective should be evaluated and deleted when an acceptable alternative is identified.

To maintain the formulary, regularly scheduled meetings must be established and attended by committee members. Ideally, the committee would meet monthly or, at the very least, every four months. Longer meeting intervals will necessitate too many agenda items and make accomplishing the necessary activities difficult.

Each meeting should have an agenda, one that describes exactly what will be addressed during the meeting. Minutes are taken and reviewed at the next scheduled meeting.
Typically, an effective DTC will provide the following at each session—

- Action on newly requested medicines and deletions (in most cases the addition of a new medicine should lead to the deletion of a similar medicine on the formulary)
- Systematic review of therapeutic groups or classes by a competent physician or pharmacist
- Review of activities to identify and resolve medicine use problems

Without this review process, the formulary may become a collection of older medicines that may not reflect the most effective products available. It is the DTC’s responsibility to see that review is accomplished regularly.

**Process for Selecting New Medicines**

Selecting medicines for the formulary should follow carefully considered policies and procedures for determining the most useful medicines. These policies should be followed routinely and accurately each time an evaluation is needed.

1. A request for addition of a medicine to the formulary, which can be made only by a physician or pharmacist, is done by completing a “Request for Addition/Deletion” form. Information needed from the physician or pharmacist includes—

   - List of specific pharmacological actions of the medicine
   - Information on why the medicine is superior to current formulary medicines
   - Specific literature support for use
   - Background on any financial support received from the supplier or other organization

2. Medicine information resources are obtained, including primary literature, international newsletters, standard treatment guidelines, textbooks, and Internet sources. All sources of information must be credible and unbiased.

3. The evaluation is performed using established criteria (see “Selection Criteria for New Medicines” below).

4. The medication information monograph is written. The medication monograph should include details about the medicine obtained from several information sources. At a minimum, the monograph should include—

   - Pharmacology
   - Pharmacokinetics
   - Efficacy compared to placebo and other medicines
   - Clinical trial analysis
   - ADRs
• Medicine interactions
• Cost comparison
• Sources of supply (to ensure availability)

5. Formulary recommendations are developed. After a thorough research of the literature, the DTC should formulate recommendations concerning the medicines on evidence-based information. Recommendations should include dosage forms and strengths that will be purchased. If a specific manufacturer or supplier is necessary because of bioavailability problems, then this issue should be addressed in these recommendations. Specific guidelines for administration or use should also be placed in these formulary recommendations.

6. Expert opinions and recommendations should be obtained from knowledgeable and respected physicians and pharmacists. Opinions should only complement (not replace) the information provided in a medicine information search.

7. The DTC makes a formulary decision (at the DTC meeting). Information should be presented to the DTC at a regularly scheduled meeting. The DTC must vote on the recommendations as presented by the individual who performed the medicine evaluation.

8. The results of the evaluation and DTC’s recommendations and actions must be disseminated to the health care staff in the form of minutes or newsletters, or through department meetings.

Selection Criteria for New Medicines

Selecting medicines for the formulary is the most important function of the formulary system. The process, which is multifactorial, ultimately brings the best medicines to the health care system. The following represent major criteria to be considered when evaluating all new requests for addition to the formulary—

• Country disease patterns
• Efficacy, relative efficacy, effectiveness
• Safety
• Quality
• Cost and cost-effectiveness
• Medicines that are well known
• Health system personnel available to manage the medicine
• Financial resources available

Disease Patterns

The morbidity of the region needs to be assessed carefully before adding or deleting any medicines. Formulary medicines should be approved only after confirmation of actual need to treat the known diseases and medical conditions of the community. Standard treatment
guidelines must be reviewed to determine appropriate medicines for the medical conditions listed in the guideline.

**Efficacy**

Proven efficacy is one of the most important criteria in selecting new medicines for the formulary. The methods to accomplish a thorough evaluation of efficacy are presented in later sessions.

Information that accompanies a new medicine, including the package insert, pharmaceutical company literature, and advertisements, may not always provide unbiased information for evaluating the medicine in question. A comprehensive review of journal articles, especially of randomized controlled trials and from available meta-analyses, will provide the best unbiased information. Reviewing information from systematic reviews, e.g., the Cochrane Collaboration, international pharmaceutical information newsletters or bulletins, and current textbooks will provide the reviewer with additional supporting information concerning efficacy. Careful evaluation of all sources must be done to ensure that evidence of efficacy is supported by the literature and is unbiased and accurate.

**Safety**

Determining the safety of a medicine requires close attention to established information on the medicine as well as current postmarketing surveillance (provided by the manufacturer or drug regulatory agency) of the medicine’s safety record. Medicines with excellent safety records are necessary for the formulary but are not always possible to obtain. A careful risk-benefit assessment will be necessary for all medicines before they are added to the formulary.

The cost of treating ADRs is high, both in monetary terms and in lowered patient quality of care. Every effort must be made to evaluate a medicine’s safety record and its potential for adverse reactions. More information concerning safety will be presented in session 4, “Assessing and Managing Medicine Safety.”

**Quality**

The quality of a medicine that is requested for the formulary is important. Poor-quality medicines that are administered to patients may have adverse effects, including—

- Lack of therapeutic effect
- Toxic and adverse reactions
- Waste of financial resources
- Loss of credibility of the health care services

Before adding a medicine to the formulary, the DTC must determine if the following characteristics of quality can be assured by the health care system—

- Identity—Active ingredients are in the dosage form.
• Purity—The medicine contains no contaminants.

• Potency—The medicine has enough, but not too much, of the active ingredient.

• Uniformity of dosage form—The consistency, color, shape, and size of tablets, capsules, creams, and liquids do not vary from one dose to the next.

• Bioavailability—Bioavailability refers to the speed and completeness with which a medicine administered in a specific form enters the blood stream; different manufacturers of the same medicine may produce medicines with different bioavailabilities.

• Stability—A pharmaceutical product must retain its properties within specified limits to be useful.

The purpose of a quality assurance program for hospitals and clinics is to ensure that every medicine reaching a patient is safe, effective, and meets quality standards. A comprehensive quality assurance program includes both technical and managerial activities from selection to patient use. Many areas within a health care system may be involved with quality assurance, including procurement, pharmacy, medical, and nursing departments, as well as the DTC.

Ensuring quality of a product is twofold—

• Obtaining quality products that are safe and effective through structured selection and procurement methods

• Maintaining quality products through the appropriate storage, distribution, monitoring, and prescribing methods

A comprehensive medicine quality assurance program requires procurement, pharmacy, and warehousing departments and the DTC to ensure the following—

• Suppliers with acceptable quality standards are selected.

• Minimum quality standards are met or exceeded and appropriate testing of the end product is performed.

• Repackaging of supplies maintains quality.

• Storage and transportation conditions are adequate.

• Product quality concerns reported by prescribers, dispensers, and consumers are documented, investigated, and resolved.

More information on medicine quality will be presented in session 5, “Pharmaceutical Quality Assurance.”
**Cost and Cost-Effectiveness**

The cost of a medicine in relation to its benefits is an important consideration with any new product. A medicine with questionable efficacy or benefits at a high cost would have an unfavorable cost-effectiveness ratio. A new antihypertensive medicine with good comparative efficacy, decreased incidence of ADRs, and a lower overall cost than current medicines on the formulary, however, would represent a medicine with excellent cost-effectiveness relationship. This medicine would therefore have a favorable status for being added to the formulary. When a new medicine with equal efficacy and possibly fewer adverse side effects at a higher cost is requested, however, the decision becomes more complicated. More information on determining the cost of pharmaceuticals is presented in session 6, “Evaluating the Cost of Pharmaceuticals.”

**Medicines That Are Well Known**

Ideally, medicines that are selected for the formulary are ones that are well known, have been on the market for years, and have clinical experience to support their pharmacological profiles. This ideal is not attainable for all medicines added to the formulary, but it should be one of the basic parameters to consider when adding a medicine.

**Availability of Appropriate Personnel**

Having available health care personnel who have the experience, training, and credentials necessary to use these medicines is important. Any medicine, no matter how effective and safe, must be measured against the personnel who will actually be using it. For example, certain antiretroviral medicines should be limited to facilities where trained physicians are available to prescribe and monitor them. A system of layered prescribing authority is useful when the health care system has practitioners with different levels of experience and qualifications. Use of vancomycin, for example, should be restricted only to senior physicians and not allowed for mid-level providers; antineoplastic medicines should be limited to facilities that have oncology expertise.

**Availability of Financial Resources**

The health care system must have at its disposal a sufficient amount of money to actually purchase and maintain the medicine for an indefinite amount of time. A thorough cost analysis is therefore necessary before the medicine is actually accepted for the formulary. If the resources are not available for the consistent procurement of a new medicine, then it should not be accepted. Intermittent purchase of a medicine that the system cannot afford only serves to foster poor medical services with little or no continuity of care. For example, the addition of a new and expensive calcium channel blocking agent for hypertension should be questioned if financial resources are not available to consistently procure the medicine. Intermittent stocking of such a medicine would lead to poor continuity of care.
Nonformulary Medicines

Most formulary systems are designed as “open” systems. The open system allows for the introduction of nonformulary medicines on a limited basis, usually for a single patient use. A “closed” system reflects the DTC’s choice to exclude all nonformulary medicines from being available in any form.

Nonformulary medicines are usually necessary, in limited amounts, for patients who require specialized treatments or patients who have been stabilized on medicines from practitioners outside of the health care system.

Control of nonformulary medicines is important because an open system will invariably become problematic and impede the system of formulary management. Numerous nonformulary medicines will be costly, and because they may not have received the complete evaluation process, they may be less than effective or unsafe. Management of nonformulary medicines includes—

- Limiting the number of nonformulary medicines
- Limiting access to appropriate prescribers
- Keeping a register of all requests for nonformulary medicines
- Reviewing frequently and discussing at DTC meetings

Policies and procedures on how these medicines will be purchased are necessary, and close follow-up of all nonformulary medicines by the DTC is warranted to limit their use.

Restricted Medicines

Restricted medicines include those products that fill a particular need by a specialty within the health system. These medicines need to be defined by the DTC to limit their use. Some examples of restricted medicines and their applicability include—

- Certain antibiotics for infectious diseases (e.g., ceftriaxone)
- Antipsychotic medicines for use by mental health professionals (e.g., use of risperidone can be restricted to psychiatrists)
- Antineoplastic products for use by physicians with specialized knowledge of these medicines

The use of restricted medicines requires close monitoring and evaluation. Monitoring of restricted medicines should include determining that appropriate patients are receiving the medicines and that authorized medical staff are prescribing and providing follow-up for patients on these medications.
International Nonproprietary Pharmaceutical Names

The use of international nonproprietary names (INNs, i.e., generic names) is encouraged for all listings in the formulary, evaluation monographs, and all other communications about medicines. The INN is the medicine’s official name, regardless of who manufactures or markets it.

Formulary systems that use the generic name system will find that it makes for a more efficient system and causes less confusion about the actual products listed. Instead of dealing with 10 to 20 (or even more) trade names for each pharmaceutical entity, there will be only one. This system will also enhance any therapeutic or generic substitution programs that may exist.

Information Resources for Evaluating New Medicines

Adequate resources to obtain information and to evaluate the efficacy, safety, quality, and cost of a medicine are essential. This section provides basic information concerning well-known medicine information sources.

Medical information sources include three categories: primary, secondary, and tertiary resources.

- Primary resources
  - Includes journal articles and unpublished studies that may be obtained from journals and services that provide the entire article
  - Advantage: represents the most complete information about a subject because all the data discussed in the article are available to the reader
  - Disadvantage: the reader must have skills to evaluate the article and the amount of time necessary to actually read and analyze it

- Secondary resources
  - Includes indexing and abstracting services that provide abbreviated reviews of articles; usually published in newsletters, CD-ROM databases, and online services
  - Advantage: readily accessible and easy-to-read information
  - Disadvantage: long period between publication and the republication in the newsletter or abstracting service

- Tertiary resources
  - Include published textbooks, which can be an excellent source of information if reputable and current sources are used
- **Advantage:** readily accessible information and short time in reading and assimilating the information

- **Disadvantages:** the lack of access to the original information sources, bias introduced by the writers of the text, and outdated information provided because of long delays in publishing a text

Representative journals and texts are listed below. There are others, but these are generally considered to be representative of excellent resources. Some journals such as *New England Journal of Medicine (NEJM)* and *Journal of the American Medical Association (JAMA)* have a policy that original research articles are available to the public at no cost six months after publication.

- **Primary resources**
  - *British Medical Journal (BMJ)*
  - *Lancet*
  - *NEJM*
  - *(JAMA)*
  - *Annals of Internal Medicine*
  - *American Journal of Health-System Pharmacy (AJHP)*

- **Secondary resources**
  - *Medical Letter*
  - *Australian Prescriber*
  - *Journal Watch*
  - *MEDLINE/PUBMED abstracts*
  - *Cochrane Library abstracts and evaluations*
  - *International Pharmaceutical Abstracts*
  - *International Society of Drug Bulletins*

- **Tertiary resources**
  - *Martindale: The Extra Pharmacopoeia*
  - *British National Formulary*
  - *United States Pharmacopeia Dispensing Information (USP DI) Drug Information for the Health Care Professional*
  - *American Hospital Formulary Service (AHFS)*

- **Internet resources**
  - *MEDLINE—www.nlm.nih.gov*
  - *WHO—www.who.int*
  - *U.S. Centers for Disease Control and Prevention—www.cdc.gov*
  - *U.S. National Institutes of Health—www.nih.gov*
  - *U.S. Food and Drug Administration—www.fda.gov*
  - *Cochrane Collaboration—www.cochrane.org*
  - *Agency for Healthcare Research and Quality—www.ahrq.gov*
  - *Others—a complete list will be provided during the training course*
Ideally, the hospital will have access to some kind of pharmaceutical information service to handle requests concerning the addition of new medicines to the formulary. If not, a pharmacist or a physician can provide the necessary evaluations given the time and at least some of the resources listed above. Pharmacists will find that, by using as many of the resources as possible, they will be able to provide the review in a comprehensive manner.

Using information from pharmaceutical companies requires the reader to exercise some caution. These companies may provide somewhat biased information. Many articles and documents may appear to provide usable information, but frequently the information presented is positive about the company’s product.

Participants should note the phenomenal changes that are occurring in the pharmaceutical information resources on the Internet. Although this communication method may not be available to pharmacists or physicians in many parts of the world, it is something to establish if at all possible. The information sources on the Internet are virtually endless. The quality of medicine evaluation reports can improve and, with experience, the speed of providing an evaluation will also improve. The Internet can also provide very poor information, so it must be used with caution.

**Formulary Manual**

The formulary manual is the publication that brings all of the data concerning the formulary together in a manual or pamphlet. There is no set standard on how this document is arranged or what it includes, but ideally it contains both alphabetically and therapeutically arranged lists of the formulary medicines and a section on medicine usage that includes doses, contraindications, side effects, medicine interactions, and price. The manual should include a section on the medicines of choice and alternatives for treating the medical conditions of the region.

This manual is not intended to be a book that is kept on the shelf. It should be pocket-sized to allow practitioners to carry it with them at all times. The design of the manual requires that it be easy to use with appropriate indexing to facilitate location of necessary information.

The following items should be available in a comprehensive formulary manual. The DTC would have to evaluate these items and include only the most appropriate in its formulary manual.

Basic information—

- **Formulary list or essential medicines list**—both alphabetical and therapeutic category lists
- **Brief information about each medicine** (i.e., a medicine monograph)
  - Generic name
  - Dosage and strengths
  - Indications
  - Contraindications
Miscellaneous information—

- Supplementary information for medicines
  - Price
  - Regulatory category
  - Storage guidelines
  - Patient counseling information
  - Labeling information
  - Brand names and synonyms

- Prescribing and dispensing guidelines
  - Rational prescribing techniques
  - Principles of prescription writing
  - Guidelines on quantities to be dispensed
  - Control medicine requirements
  - ADR reporting requirements
  - Dispensing guidelines
  - List of precautionary labels
  - Medicine interaction tables

- Treatment protocols
  - IV medicine administration guidelines
  - Medicines used in pregnancy and lactation
  - Medicines used in renal failure
  - Poison guidelines
  - Prescribing for the elderly

- Other components
  - Metric tables
  - ADR form
  - Product quality report form
  - Formulary request form
  - Nonformulary request forms
  - Abbreviations
  - Indexes—A comprehensive index of all items in the formulary manual is essential. Because of the complexity of this document, an index will facilitate use by practitioners and ultimately improve efficiency within the health care system.

Formulary manuals require a meticulous approach to developing and publishing the document. Like a standard treatment guideline, a formulary manual requires buy-in from opinion leaders,
administration, senior medical staff, and local professional associations. Manuals must be prepared carefully using only evidenced-based information; they must be written by experts and reviewed frequently to maintain up-to-date information.

**Activity 1. Adding a New Antimicrobial to the Formulary**

Your DTC is considering a new antibiotic for the formulary. This antibiotic, which we’ll call *cefapime*, is very similar to a formulary product, cefotaxime, a third-generation cephalosporin. It would be used in the emergency room as a single dose for treating febrile children with the diagnosis of acute respiratory infection or otitis media. This medicine is an injectable at a high cost of 2.50 U.S. dollars (USD) per dose. Although expensive, cefapime is required (according to the requesting physician) because of a high incidence of antimicrobial resistance (AMR) in the hospital to commonly used medicines. The physician also states that use of the medicine will decrease overall cost because hospitalizations of these sick children will be decreased with appropriate use. Mid-level providers who staff the emergency room at night would be the primary prescribers of this medicine. This medicine is heavily promoted by a pharmaceutical manufacturer for treating many different pediatric infections. Other medicines for these problems that are available on the formulary include amoxicillin, co-trimoxazole, and cefalexin. Typically the DTC has provided very little evaluation of a new medicine because a physician’s recommendation was enough for approval by the committee.

Consider the following questions—

- What criteria are necessary to evaluate this medicine for addition to the formulary?
- Using the principles of formulary management discussed in this session, what major concerns do you have before adding this medicine to the formulary?
- What drug information resources would be used to analyze this medicine for the DTC? Which source would be the most useful?

**Activity 2. Analyze the Quality of a Formulary—the Case of NSAIDs**

Below is a list of nonsteroidal anti-inflammatory drugs (NSAIDS) from the formulary of a large private hospital in East Africa. Ask the participants to use the principles of formulary management learned in this session to answer the following questions about this category of medicines (possible answers are in italics below the list)—

- Do you think the listed medicines appear logical and well chosen?
- How many chemical entities are available on the formulary?
- How many NSAID medicines are necessary for a formulary?
- What medicines would you recommend be added or deleted?
- What is the best method to list medicines in a formulary? Is this list easy to read and understand?

<table>
<thead>
<tr>
<th>No.</th>
<th>NSAID</th>
<th>Quantity Sold (over 6 months)</th>
<th>Unit Cost (USD)</th>
<th>Total Cost (USD) (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LYSINE ACETYL SALICYLIC ACID 500 mg</td>
<td>2,026</td>
<td>0.357</td>
<td>723.54</td>
</tr>
<tr>
<td>2</td>
<td>ASPEGIC (lysine acetylsalicylic) 1,000 sachet ADULT</td>
<td>27</td>
<td>0.264</td>
<td>7.14</td>
</tr>
<tr>
<td>3</td>
<td>ASPEGIC 250 mg sachet INFANT (lysine acetylsalicylic acid)</td>
<td>40</td>
<td>0.126</td>
<td>5.05</td>
</tr>
<tr>
<td>4</td>
<td>ASPEGIC sachets (lysine acetylsalicylic acid) 100 mg</td>
<td>51</td>
<td>0.109</td>
<td>5.56</td>
</tr>
<tr>
<td>5</td>
<td>ASPIRIN tablets 500 mg</td>
<td>237</td>
<td>0.004</td>
<td>0.90</td>
</tr>
<tr>
<td>6</td>
<td>ASPIRIN tablets 100 mg (1)</td>
<td>1,877</td>
<td>0.002</td>
<td>2.84</td>
</tr>
<tr>
<td>7</td>
<td>ASPIRIN tablets 300 mg (1)</td>
<td>1,190</td>
<td>0.002</td>
<td>2.44</td>
</tr>
<tr>
<td>8</td>
<td>ASPIRIN tablets 80 mg</td>
<td>3,145</td>
<td>0.002</td>
<td>4.86</td>
</tr>
<tr>
<td>9</td>
<td>DICLOFENAC 100 mg SR</td>
<td>8,475</td>
<td>0.016</td>
<td>135.88</td>
</tr>
<tr>
<td>10</td>
<td>DICLOFENAC ampule ADCO 75 mg/3 ml (1)</td>
<td>7,797</td>
<td>0.061</td>
<td>477.61</td>
</tr>
<tr>
<td>11</td>
<td>DICLOFENAC gel</td>
<td>188</td>
<td>0.380</td>
<td>71.46</td>
</tr>
<tr>
<td>12</td>
<td>DICLOFENAC ointment 30 g</td>
<td>5</td>
<td>0.364</td>
<td>1.82</td>
</tr>
<tr>
<td>13</td>
<td>DICLOFENAC suppositories 100 mg</td>
<td>22,186</td>
<td>0.077</td>
<td>1,707.56</td>
</tr>
<tr>
<td>14</td>
<td>DICLOFENAC tablet 50 mg</td>
<td>23,835</td>
<td>0.006</td>
<td>133.71</td>
</tr>
<tr>
<td>15</td>
<td>IBUPROFEN syrup 100 mg/5 ml (60 ml)</td>
<td>3,080</td>
<td>0.498</td>
<td>1,533.65</td>
</tr>
<tr>
<td>16</td>
<td>IBUPROFEN tablet 200 mg (1)</td>
<td>85,197</td>
<td>0.004</td>
<td>320.16</td>
</tr>
<tr>
<td>17</td>
<td>INDOMED capsules 25 mg (1)</td>
<td>4,199</td>
<td>0.003</td>
<td>11.45</td>
</tr>
<tr>
<td>18</td>
<td>KETOPROFEN 150 mg (1)</td>
<td>128</td>
<td>0.427</td>
<td>54.69</td>
</tr>
<tr>
<td>19</td>
<td>MEFENAMIC ACID 500 mg</td>
<td>2,328</td>
<td>0.198</td>
<td>460.84</td>
</tr>
<tr>
<td>20</td>
<td>MEFENAMIC capsules 250 mg</td>
<td>37</td>
<td>0.044</td>
<td>1.61</td>
</tr>
<tr>
<td>21</td>
<td>NAPROXEN tablets 250 mg</td>
<td>252</td>
<td>0.340</td>
<td>85.63</td>
</tr>
<tr>
<td>22</td>
<td>NIFLURIL POMMADE (niflumic acid)</td>
<td>634</td>
<td>3.091</td>
<td>1,959.73</td>
</tr>
<tr>
<td>23</td>
<td>NAPROXEN tablets 250 mg</td>
<td>252</td>
<td>0.340</td>
<td>85.63</td>
</tr>
<tr>
<td>24</td>
<td>NIFLURIL (niflumic acid) capsules 250 mg (1)</td>
<td>1,537</td>
<td>0.119</td>
<td>182.52</td>
</tr>
<tr>
<td>25</td>
<td>NIFLURIL cream topical (niflumic acid)</td>
<td>649</td>
<td>2.186</td>
<td>1,419.02</td>
</tr>
<tr>
<td>26</td>
<td>NIFLURIL suppositories 700 mg (ADULT) (niflumic acid)</td>
<td>1,319</td>
<td>0.305</td>
<td>402.08</td>
</tr>
<tr>
<td>27</td>
<td>NIFLURIL suppositories (INFANT) (niflumic acid) 400 mg</td>
<td>314</td>
<td>0.258</td>
<td>81.13</td>
</tr>
<tr>
<td>28</td>
<td>NAPROXEN tablets 250 mg</td>
<td>252</td>
<td>0.340</td>
<td>85.63</td>
</tr>
<tr>
<td>29</td>
<td>NIMESULIDE tablets 100 mg</td>
<td>22,260</td>
<td>0.038</td>
<td>848.67</td>
</tr>
<tr>
<td>30</td>
<td>PIROXICAM 20 mg</td>
<td>643</td>
<td>0.021</td>
<td>13.37</td>
</tr>
</tbody>
</table>
Summary

The formulary system adds an important component to the DTC and the health care system. A system of evaluating and selecting the most appropriate medicines for the formulary will bring numerous benefits. These include rational use of medicines, improved health care outcomes, improved efficiency in the procurement and inventory management systems, regular supply of essential medicines, and a significant decrease in overall health care cost.

Listed below are some key guidelines to remember to start a formulary system or maintain one for years to come—

- Write detailed policies and procedures concerning the functions of the formulary system.
- Follow formulary management principles to obtain the best medicines at a favorable cost.
  - Medicines should be selected based on the needs of the community; they should treat the diseases and conditions that have been identified locally.
  - Medicines selected for the formulary are “medicines of choice.”
  - The formulary list should have a limited number of medicines, only those necessary to provide for the needs of the hospital or clinic; duplication of agents that have therapeutic equivalence should not occur.
  - Use INN (i.e., generic names).
  - Use combination (fixed-dose) products only in specific proven conditions (e.g., to treat tuberculosis).
  - Medicines need to be selected based on explicit criteria that include proven efficacy, safety, quality, and cost.
  - The formulary must be consistent with any national or regional formulary or approved standard treatment guidelines.
- Review the formulary in a systematic manner to ensure it is current.
- Keep the number of nonformulary medicines to a minimum.
- Restrict medicines to appropriate practitioners.
- Maintain reliable resources (human, financial, references) for the evaluation of medicines.
• Keep the formulary process ethically correct—the DTC and especially the formulary system must tolerate no influence or pressure from pharmaceutical manufacturers or suppliers concerning any product that is considered for addition to or deletion from the formulary.

• Enlist support of key policy makers and influential health professionals to advocate for the DTC and the formulary system
Drug and Therapeutics Committee
Training Course

Session 3.
Assessing Medicine Efficacy
SESSION 3. ASSESSING MEDICINE EFFICACY

Purpose and Content

Session 3 is designed to provide participants with a basic guide on how to determine medicine efficacy, primarily through review of the pharmaceutical literature with an emphasis on evaluating randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Systematic and thorough evaluations of the pharmaceutical literature will provide the Drug and Therapeutics Committee (DTC) with the unbiased information necessary to select appropriate medicines for the formulary.

In most countries, evaluating the pharmaceutical literature is commonly done by physicians and pharmacists. Unfortunately, this review is often done incorrectly. With the tools presented in this session and practice at home, participants will be better equipped to evaluate the literature systematically and scientifically.

Objectives

After attending this session, participants will be able to—

- Understand the importance of determining efficacy and evaluating the clinical literature
- Discuss the major types of medicine study design
- Describe the key components of a journal article
- Understand how to evaluate and interpret results of a randomized controlled trial
- Discuss the use of systematic reviews and meta-analyses in evaluating medicines

Preparation and Materials

Read the following—

- This session—A thorough understanding of this session is necessary before the presentation.
- Review session 2, “Developing and Maintaining a Formulary” of the Participants’ Guide.
- Activity article—Randomized trial of artesunate and mefloquine alone and in sequence for acute uncomplicated falciparum malaria.
Further Readings


Introduction

There are thousands of drugs on the market in most countries. If an effective drug regulatory system is in place, there will have been some assessment of the quality, safety and efficacy of the drugs that are registered, but no single hospital or health care facility can afford to provide all the registered products. One of the key roles of a DTC, therefore, is to ensure that a selected list of medicines is provided. Medicines need to be selected so that the formulary—

- Meets the needs of the population being treated by the health facility
- Includes medicines that are effective and safe
- Includes medicines that are the most cost-effective of those that are available.

Every DTC needs to have a standard selection process for adding medicines to the formulary. The first consideration is whether the medicine being proposed is at least as effective as those currently being used for the same purpose. Making this judgment requires consideration of clinical trial evidence, which is complex and time consuming but critical for the effective functioning of a DTC.

Ideally, selection of a list of medicines should be closely aligned with standard treatment guidelines that are used locally for managing patients with the diseases that are important in the particular area, but often, DTCs are asked to consider new medicines that are not in the guidelines or medicines for conditions for which standard treatment guidelines do not exist.

This session covers the methods of assessing clinical evidence, including some information about different types of clinical studies, how to assess whether clinical trials are reliable and how to interpret the results of clinical studies including some important statistical concepts. These
skills require time and practice to acquire, but are essential for DTCs to adequately assess drugs for addition to the formulary.

**Formulating the Question**

The first step in assessing whether a new drug is effective is to formulate the *clinical question* that is important to your DTC. This should be constructed to specify—

- The patient **population** (P)
- The drug **intervention** you are interested in (I)
- The **comparative** treatment already available (C)
- The **outcome** that is important to clinicians and patients (O)

For example: In diabetic patients over age 60 (P), does metformin (I) compared to glibenclamide (C) reduce the risk of stroke (O)?

A well constructed clinical question means that—

- Your librarian, if you have one, or your pharmacist, or you can *search* the medical literature efficiently for relevant evidence.
- Your DTC can *review* only the evidence that is relevant, rather than being snowed under with many articles, reports, text book reviews, etc.!
- If the drug is added to your list, the drug’s use can be targeted to the indication and patients you have specified in your question, and vice versa; new products can be considered very specifically for precise purposes, rather than the broader approach of should we add metformin to our list.

**Finding the Evidence**

Once the DTC has considered the clinical question (which should be part of the proposal for any new product) there is a need to find the relevant clinical evidence. Depending on your resources, you may decide to ask for relevant clinical evidence to be submitted with the proposal to add a new drug, or you might have a member of the DTC undertake an independent search of the medical literature to find it. With an increasing availability of open access online databases of clinical studies, an independent review may offer the best approach, but it will take time!

There are many standardized ways now of searching databases such as PubMed and Medline to find clinical trials, systematic reviews, and summaries about new products. The important consideration is that, however the search is done, it attempts to find all relevant studies, not just a selection of information that presents the drug in the best light.
What Sort of Evidence?

When we are talking about “clinical evidence” what exactly is meant? Articles published in reputable medical journals generally fall into one of four different types—

- Secondary research or reviews, which can be—
  - *Overviews*—usually non-systematic summaries of the literature on a particular topic, often heavily influenced by the opinion of the author
  - *Systematic reviews*—these are comprehensive and rigorous summaries of all the studies done on a particular topic, that may include statistical combination of the results of all the studies (meta-analysis) to come up with an overall estimate of the effect of one drug compared with something else
  - *Economic analyses*—a study that describes the costs and effects of a particular treatment or health care intervention

- Clinical trials, in which an intervention such as a drug treatment is given to a group of patients and compared to the effects of some other treatment

- Surveys, in which something is measured in a group of patients or some other sample of individuals

- Experiments, where some sort of maneuver (sometimes a drug treatment) is given to humans (or animals) in an artificial or controlled environment

For a DTC, the evidence that is most reliable to use to evaluate whether a new drug is effective is a systematic review that contains several randomized clinical trials and a meta-analysis. For evaluation of drug safety, additional studies may be needed. But the medical literature still contains many studies that have major flaws and are therefore unreliable, so it is important to be able to judge whether a study of any type is of good enough quality to be used as the basis of a drug choice. The systematic assessment of medical publications is known as critical appraisal and the next sections of this module will cover the basic approach to appraising an individual study as well as a systematic review.

Assessing the Quality of the Evidence—What Makes a Good Clinical Trial?

Most studies that report a clinical trial that are published in medical journals are in a standard format that has been adopted by the journal editors.

- *Abstract* (which also has a standard structure in many journals)
- *Introduction* (why the authors decided to do this research)
- *Methods* section (how they did it and how they analyzed their results)
- *Results* section (what they found)
- *Discussion* (what the results mean, in the opinion of the authors)
An example of an abstract in a high quality journal is shown in Box 1. There will also be an Acknowledgments section and a list of references. Judgments about the quality of a paper should be made on the basis of an assessment of the “Methods” section, not on the interest of the title or hypothesis or what the authors think the results mean.

**Box 1. Structure Abstract (Source: Journal of the American Medical Association, 2005)**

**Context** The SYNERGY trial comparing enoxaparin and unfractionated heparin in high-risk patients with acute coronary syndromes (ACS) showed that enoxaparin was not inferior to unfractionated heparin in reducing death or nonfatal myocardial infarction (MI) at 30 days.

**Objective** To evaluate continued risk in this patient cohort through 6-month and 1-year follow-up.

**Design, Setting, and Patients** Overall, 9978 patients were randomized from August 2001 through December 2003 in 487 hospitals in 12 countries. Patients were followed up for 6 months and for 1 year.

**Main Outcome Measures** Six-month outcomes were death, nonfatal MI, revascularization procedures, stroke, and site-investigator– reported need for re-hospitalization; 1-year outcome was all-cause death.

**Results** Six-month and 1-year follow-up data were available for 9,957 (99.8%) and 9,608 (96.3%) of 9,978 patients, respectively; 541 patients (5.4%) had died at 6 months and 739 (7.4%) at 1 year. Death or nonfatal MI at 6 months occurred in 872 patients receiving enoxaparin (17.6%) vs. 884 receiving unfractionated heparin (17.8%) (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.89-1.07; \( P = .65 \)). In the subgroup of patients receiving consistent therapy, that is, only enoxaparin or unfractionated heparin during the index hospitalization (n=6138), a reduction in death or nonfatal MI with enoxaparin was maintained at 180 days (HR, 0.85; 95% CI, 0.75-0.95; \( P = .006 \)). Re-hospitalization within 180 days occurred in 858 patients receiving enoxaparin (17.9%) and 911 receiving unfractionated heparin (19.0%) (HR, 0.94; 95%CI, 0.85-1.03; \( P = .17 \)). One-year all-cause death rates were similar in the two treatment groups (380/4,974 [7.6%] for enoxaparin vs. 359/4,948 [7.3%] for unfractionated heparin; HR, 1.06; 95% CI 0.92-1.22; \( P = .44 \)). One-year death rates in patients receiving consistent therapy were also similar (251/3,386 [7.4%] for enoxaparin vs. 213/2,720 [7.8%] for unfractionated heparin; HR, 0.95; 95% CI, 0.79– 1.14; \( P = .55 \)).

**Conclusions** In the SYNERGY trial, patients continued to experience adverse cardiac events through long-term follow-up. The effect of enoxaparin on death or MI compared with that of unfractionated heparin at 6 months was similar to that observed at 30 days in the overall trial and in the consistent-therapy group. One-year death rates were also similar in both groups. High-risk patients with ACS remain susceptible to continued cardiac events despite aggressive therapies.

**ClinicalTrials.gov Identifier:** NCT00043784.

*JAMA. 2005; 294:2594-600 www.jama.com*

There should be a statement about who funded the study. Sometimes this is in the Acknowledgments section only, but increasingly there will also be a description of the funding arrangements and the role of the funding source in the Methods section of the paper. This is important as it has been shown repeatedly that the funding arrangements for a study can have a big influence on the results.

There should also be a statement about the author’s affiliations and potential conflicts of interest as well as their individual contributions to the study and the report. If a study is funded by a pharmaceutical company and all the authors are employees and there was no independent investigator, analysis or review, it may be biased and probably not worth spending too much time on!
So you have decided to try to read the paper that you have found and critically appraise it to determine whether the results are reliable and valid and can be used by your DTC to make a decision about a drug. Where do you start? Ideally you should develop a systematic approach that you use for every study. There are many checklists of questions for evaluating scientific articles, but these ones below offer a simple and comprehensive approach, and have been widely used in learning and teaching evidence-based medicine (Greenhalgh 1997). Most of these questions should be able to be answered after a careful reading of the Methods section of a current paper.

**Why Was the Study Done? What Clinical Questions Were the Authors Addressing?**

In a research paper, the introductory sentence should give a summary statement of what the background to the study is. For example, “Use of antibiotics for the treatment of upper respiratory tract infections in children is very common but it has been suggested that mostly the antibiotics are not necessary.” You should then be able to find, either in the introduction or methods section, a statement of the hypothesis that the authors have decided to test. This statement might be, “Antibiotics do not improve the symptoms and recovery time of upper respiratory tract infections in children.” If it is presented in the negative like this example, it is known as a *null* hypothesis. Authors generally set out to disprove this hypothesis in their study.

**What Type of Study Was Done?**

There are many different types of studies and different ways of conducting them. As noted above, most published articles will be either reports of reviews, experiments, trials, or surveys. For each of these types of studies there are important features to look for in the design of the study. The first point to check is whether there is an *intervention* that is being tested, such as a drug, operation, or diagnostic procedure, or whether the authors are reporting the results of an *observational* study, that is, where they did not have control of what happened to the patients or subjects.

For studies testing whether new interventions are effective, the most reliable design is a randomized comparative trial, where the patients being studied are allocated by chance to either the new intervention that is being tested, or the alternative comparative treatment. Sometimes the comparative treatment is a placebo drug or procedure; sometimes it is the best treatment that is currently available. If the authors are testing a new intervention and have *not* used a randomized trial as their design, it is very important to consider why they have not done so, as it is likely that the result will be biased in favor of the new treatment. A typical diagram describing a randomized trial is shown in Box 2 below.
Ideally, any new drug that is being considered by a DTC should have been studied in several randomized controlled trials, which have then been summarized objectively in a systematic review.
For studies that are reporting the results of observations, there are generally three types—

- **Cohort studies.** These studies involve groups of patients or subjects are observed over a period of time. The period can range from an observation at a single time point\(^7\) to repeated observations over many years. Each cohort of patients or subjects should be defined in advance on the basis of common features. There are many ways of doing this, for example, geographical and date inclusion criteria (e.g., all patients living in a certain suburb in a certain year); criteria related to characteristics of a disease, or exposure to a common event (e.g., all employees of a factory closed on a certain date). The important feature to consider is whether the authors have specified these inclusion criteria in advance and have made reasonable efforts to ensure that all appropriate subjects have in fact been included. For a DTC, cohort studies can be useful in assessing safety of new drugs, and sometimes they can also provide helpful information about how drugs are used in practice. However, they are not a reliable source of information for assessing whether a new drug is effective.

- **Case-control studies.** These are studies where the authors have firstly defined a “case” that they are investigating, which is a particular outcome or event in a subject (such as admission to hospital because of a gastrointestinal hemorrhage). The authors then compare the frequency of exposure to a substance of interest (e.g., aspirin) in a group of “cases,” with the frequency of exposure to the same substance in a group of “controls,” that is subjects who do not have the outcome being studied. Such studies are complex and difficult to perform well without bias, but when done correctly, they can be extremely useful in assessing whether rare adverse events are caused by exposure to a particular drug or substance.

- **Case reports.** These are studies that usually report the experience of an individual doctor in relation to a patient or group of patients with the same disease, or treatment. The classic example of the value of case reports is the first case report of thalidomide causing limb deformities. This case report could not be used to prove that thalidomide was the cause, but it acted as a warning signal that was followed up in a number of case control studies that did establish the relationship beyond reasonable doubt. Case reports therefore provide valuable anecdotal information about individual events and can therefore be helpful in assessing the safety profile of a drug, but cannot be used to assess drug efficacy.

**Was the Study Design Appropriate to the Research Question?**

To answer this question, it is helpful to categorize the field of research in the paper that you are considering as one of the following types. You should then consider whether the study design used is the preferred design for the research question.

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\(^7\) The difference between a cross-sectional study and a cohort study with observed measurement at a single point in time is that in the cohort study, the patients are defined in advance on the basis of common features and in the cross-sectional study the patients are not so defined in advance.
• Therapy (testing efficacy of drug treatments, surgical procedures, ways of delivering care)—preferred design is a randomized controlled trial

• Diagnosis (is a new diagnostic test valid and reliable)—preferred design is a combination of a randomized comparison of the new test with the old plus follow-up of a cohort or patients

• Screening (can a diagnostic test pick up a disease at a pre-symptomatic stage in a large population, and can that lead to better outcomes from treatment of the disease)—preferred design is a cross-sectional cohort survey

• Prognosis (what is the outcome of a disease over time)—preferred design is a longitudinal cohort study of patients with the disease

• Causation (is a particular agent—toxin, drug, environmental factor—related to the cause of a disease)—preferred design is a case control or cohort study

Was the Design of the Study Sensible?

A study can be the preferred design for the type of research and research question, but can still be designed in a way that reduces the usefulness and reliability of the results. There are two important aspects of study design to consider first.

• Exactly what specific intervention was being considered and what was it compared with? For studies of new drugs, do the authors describe exactly the dose, preparation, frequency and nature of administration, for example? Is the comparator something that is accepted as current best practice, or a reasonable alternative? For example, it would not be reasonable to compare a new product for hypertension with a half-dose of an ACE inhibitor, or drugs no longer used because of side effects, such as reserpine.

• What outcome was measured in the study, and how? Is it an outcome that is important to clinicians and patients, or is it a physiological measurement that has little connection with patient survival or quality of life? In drug trials particularly, there is a tendency for authors to measure either “surrogate outcomes,” that are supposed to be proxies for clinically relevant endpoints but may or may not be truly so. An alternative strategy that is used to boost a medicine’s chances of being “successful” is for authors to measure “composite outcomes,” such as the frequency of “death OR heart attack OR chest pain” in patients treated with the new and the old intervention. The problem with this approach is that often the effect of the drug is mainly on one, but not all, of these endpoints and they are all treated with equal importance by the investigators, which may not be clinically appropriate.

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8 A cross-sectional cohort study is where a source population is sampled cross-sectionally and then the subjects' histories of exposures and outcomes are assessed retrospectively over a specified period of time. See Hudson, J. I., H. G. Pope Jr., and R. J. Glynn. 2005 The Cross-Sectional Cohort Study: An Underutilized Design. Epidemiology 16(3):355–59.
Who Is Studied?

When making decisions about new drugs a DTC needs to consider how the patients in the trial relate to those in the setting where the drug will be used. Questions to consider include the following—

- How were the subjects for the study recruited—enthusiastic volunteers only or a more representative sample of a population?

- Who was included in the study—patients with only a single uncomplicated disease or patients who have multiple illnesses and are more representative of the population in which the drug will be used?

- Who was excluded from the study—and is it likely to lead to false conclusions about the effects of an intervention due to different responses in patients with different baseline severity of disease?

- What was the setting of the study and how does it relate to the local environment? The results of an intervention based on a study in tertiary care hospital may not translate well into a primary care setting without the same level of back-up care.

How Well Was the Study Conducted? Was Systematic Bias Avoided or Minimized?

There have been many “studies of studies” carried out over the past 20 years to try to define what features within a study will produce the most reliable results. In some respects, this question is the most important part of a critical appraisal of a study. To start with some definitions—

- Bias is defined as anything that leads to deviation of the results from the truth, or processes leading to such deviation.

- Randomization—the process of assigning patients to treatment groups by chance.

- Observer-blind—the person measuring the outcomes in a study is not told what treatment patients have received.

- Double-blind—neither the observer nor the patient in a trial knows what treatment the patients received.

- Allocation—the process of assigning patients to treatment groups.

- Intention-to-treat population—the total number of patients assigned to receive a particular treatment, irrespective of whether they actually received it or not.
• Confounding factor/variable—a variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation.

Annex 1 contains a glossary of additional terms.

**Quality of Randomized Controlled Trials: What to Look for**

There are now empirical data that show that for a randomized controlled trial, the features that are most important in determining the reliability of the results (or the likelihood of bias) are the following—

• Exactly what method was used to randomize the patients to treatment groups
• Whether both patient and observer are kept “blind” to treatment
• Whether all patients are followed up and included in the analysis

We will now deal with each of these factors in turn in more detail.

**Randomization and Concealment of Allocation**

As noted above, randomization is the process used to assign subjects in study by chance to one treatment group or another. Assigning patients by chance removes the likelihood that the investigator will select patients, either consciously or unconsciously, for the experimental treatment who are more or less likely to respond to it. This is called selection bias and we know that studies where selection bias occurs are more likely to produce results that significantly favor the experimental treatment and also overestimate the size of benefit produced by the experimental treatment. Random allocation also should result in any possible confounding factors being equally distributed between the two groups, and therefore be less likely for them to have a differential effect on the results.

It is not just enough, however, to assign patients at random to treatment groups. There are many ways this can be done. For example, by tossing a coin and using the heads or tails to determine the treatment group; by putting numbers for each treatment group in sealed envelopes and pulling them out of a drawer at random, or by having a process (used in many trials now), where once the patient consents to enter the study, the treating physician phones a centralized service, that allocates the patient to treatment based on a computer generated code without telling either patient or doctor what it is. This last method is the most reliable because is least likely to be able to be influenced by the treating doctor and therefore is regarded as the “gold standard” for clinical trials. If the paper you are reviewing does not tell you how the patients were randomized and how the allocation process was concealed, it is more likely to have unreliable results that favor the experimental treatment.

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A variable in a causal pathway that causes variation in the dependent variable and is itself caused to vary by the independent variable.
**Double-Blind vs. Open Trials**

There are three parties who can influence the trial results if they know what treatment a patient in a study is receiving: the patients themselves, the treating physician, and the person measuring the outcome. We know that if all three are aware of the treatment, then the results of the study are more likely to be biased in favor of the experimental treatment compared with the control. Various terms are used for this but the most common is *observer bias* (where the observer consciously or unconsciously influences the results). Ideally, therefore, the patient, treating doctor and observer should all be unaware of the treatment group so that any placebo should exactly match the active treatment. However, this may not always be feasible, in which case other steps should be taken to ensure that the results are as reliable as possible. These include the following—

- Making sure that the outcome is an objective, black and white event (such as death) rather than an event defined in a way that is open to subjective interpretation (such as “significant improvement in pain”).

- If possible, ensuring that the person measuring the outcome is unaware of the treatment, even if the patient and treating doctor know.

- Having dubious outcomes (for example, was the cause of death in a subject heart failure, which could have been prevented by the treatment, or was it due to a respiratory infection, unrelated to the treatment?) adjudicated by an independent committee (who are unaware of the treatment group for the patient concerned).

In summary, double blind placebo controlled trials with objective outcomes judged by an independent outcome committee are the gold standard. Less than this may practically be necessary, but will reduce your confidence in the results, and it will be a matter of judgment as to how much this matters for the assessment of an individual trial.

**Inclusion of All Patients in the Statistical Analysis**

A trial is less likely to have biased results if all patients recruited and allocated to treatment are accounted for. In the example shown in figure 1, the intention to treat (ITT) population is the 320 patients randomized to the two treatment groups, even though at the four month follow-up point there were only 230 patients left in the trial. By using the ITT population in the denominator for the analysis, the most conservative estimate of the effect of any treatment is obtained. Although in some instances this may be an underestimate, it is less likely to be subject to bias.

*Trials of new interventions that do not report what happened to all patients and do not report an ITT analysis should be treated with more uncertainty than those that do.*

Figure 1 summarizes the key sources of bias that can occur in randomized trials.
Figure 1. Summary of key sources of bias in randomized trials.

Quality of Non-Randomized Trials—What to Look for

There are fewer empirical studies that can be used to help us assess what is most important in deciding whether a non-randomized study has been done well or done poorly, but if you think about it, it should be apparent that the main difference between randomized and non-randomized studies is the likelihood that in non-randomized studies, the risk of selection bias is higher. This is such a critical difference that it tends to overwhelm all other considerations, but in assessing the quality of a non-randomized study, it is important to try to make a judgment about how much selection bias has been introduced in the process used to include subjects in the study. If, in your judgment, it is significant, then the results are more likely than not to be due to selection and confounding. Although there are statistical techniques that can be used to attempt to compensate for this, no amount of statistical adjustment can overcome the fundamental bias that is introduced by absence of randomization.
Understanding the Numbers

So you have got this far through the methods section of the paper and have decided that the study is of sufficient quality for you to persist with assessing the results. In the results there will be some statistical analyses. Before getting overwhelmed by statistical jargon, it is worth stating some basic principles. The purpose of these analyses is to determine whether any differences in outcomes that have been found in one group compared with another are real and due to the difference in treatment or whether they are simply the result of the play of chance. We cannot avoid talking about some basic statistical concepts here, but for practical purposes, there are a few key numbers to master that will greatly improve the reliability of decisions of a DTC.

We will divide these considerations into two groups—what did that authors think they were going to find, and how do we interpret what they did find?

What Did the Authors Think They Would Find?

A trial should be big enough and long enough to have a high chance of detecting, if it exists, an effect of treatment that is both clinically and statistically significant (the real effect rather than one due to chance). So somewhere in the methods section there should be a statement about the difference between the two treatments that the authors want to find and therefore an estimated sample size.

For example, if you are comparing two drugs for the treatment of high blood pressure, we know from long-term observational studies that a difference of 5 mm Hg in systolic pressure that is sustained over several months is enough of a difference to result in a change in the likelihood of stroke or cardiovascular disease. Trials comparing treatments in hypertension therefore need to include enough subjects to show a 5 mm Hg difference if it exists. It would be more reliable if strokes and cardiovascular disease were actually measured, but such a trial would need to take longer and probably be larger as well. What you as the reader are looking for is, what did the authors decide was an important difference before they did the trial and therefore (using a standardized statistical algorithm available in most statistical software packages), how many patients did they calculate they would need. Did they get that many subjects into the study or not, and if not, why not?

What Were the Results?

The key concepts for a DTC to consider in relation to understanding results of studies are as follows—

- Different types of data need different statistical tests.
- But most types of studies can be analyzed using one of a relatively few standard approaches.
- It is necessary to compare the effect of treatment in one group relative to the effect in the other.
• It is also critical to compare the absolute value of the results in one group with those in the other.

• The difference in the effects of the treatments (if any) can be described as the estimate of the effect size, and the range of plausible results is expressed in the confidence interval; the probability that the difference is real and not due to chance is expressed in the p value.

Again, some detailed discussion of each of these points follow. We cannot provide a complete statistical textbook; further reading for those of you who are interested is listed in the reference material.

**Different Types of Data Need Different Statistical Tests**

For trials of new drugs, there are four considerations. First, are there descriptive statistics that you can use to compare the different patient groups at baseline? This should include, for example, the mean age of patients in each group, perhaps the weight, the proportion of patients from different ethnic backgrounds, the proportion of patients with other illnesses, and so on. An example of a standard type of table is shown in figure 2.
Figure 2. Example of descriptive statistics for baseline characteristics.

In the table in figure 2, you can see that there are \( p \) values given for the comparison of each variable. For continuous variables, (where each value has a meaning, such as centimeters or kilograms) such as weight, the \( p \) value has been calculated from a \( t \) test. For categorical variables (the variable exists or not, e.g., current smoker), a chi-squared test has been used. All the \( p \) values are larger than 0.05, which is conventionally accepted as the cutoff value for statistical significance in most trials. A \( p \) value of 0.05 means that there is a 1 in 20 probability that the differences between the groups are due to chance alone. In this context the purpose of such comparisons is to show that as far as possible, there are no real differences between the groups at baseline that could influence the results.

The second consideration is whether the main outcome of the trial (technically this should be specified in the methods as the primary outcome) is a continuous variable or a categorical one, and whether the data are normally distributed or not. These factors then should determine what type of statistical test should be used, which will be discussed further below.
Third, the authors should have specified in the methods what their planned analysis was, both in terms of the tests to be used based on the considerations noted above, but also in terms of what groups and comparisons are to be made. For example, were they only going to compare the results of all patients in the intervention group with the control, or were they planning in advance to compare the results in men and women as well? If you do enough comparisons, you will end up with one of them having a statically significant \( p \) value by chance, so it is important that the authors plan the analyses before they get the data and do not go “data dredging” afterward.

And fourth, what \textit{metric} (numerical expression) have the authors used to describe their results for dichotomous data (outcomes with a yes/no response)?

\textbf{Understanding Metrics or the Bottom Line}

Generally, the simplest way of describing the results of a trial is to use proportions to describe the number of patients in a treatment group who have the outcome (as the numerator) compared with the total number in the group. In a theoretical trial that compares the effect of a new drug with an old one in terms of the number of people who die from heart failure after five years of treatment, the results might look like what is shown in Table 1.

\begin{table}[h!]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Group & Number of Patients Who Died & Number of Patients Who Did Not Die & Total in Each Group \\
\hline
New medicine group & 5 (a) & 95 (b) & 100 (a+b) \\
Old medicine group & 10 (c) & 90 (d) & 100 (c+d) \\
\hline
\end{tabular}
\caption{Results}
\end{table}

The risk of dying if you are treated with the old drug is 10/100 or 0.10 or 10 percent. This is also called the \textit{control event rate or control event risk}. (Strictly speaking, if you use the term \textit{rate} you should also specify the time period, e.g., per five years, but often the time frame is omitted when specifying the figures in articles or reports!)

The risk of dying within 5 years if you are treated with the new drug is 5/100 or 0.05 or 5 percent; the \textit{experimental event rate}.

As a DTC, you are interested in what the effects are in one group compared to the other. The \textit{relative risk of death} in the new drug group compared with the old is the \textit{ratio} of the experimental event rate to the control event rate—0.05/0.10 = 0.5.

That is, you are half as likely to die if you get the new drug versus the old (or you are twice as likely to die if you get the old drug rather than the new). Other terms used for this metric are \textit{rate ratio} or \textit{risk ratio}; these can be helpful reminders of how it is calculated.

As a DTC, however, you are not just interested in the \textit{relative performance} of a drug: you need to consider the \textit{absolute} benefit, which takes into account how common the events are. This is expressed as the \textit{absolute risk difference}, which as the term implies is calculated as the difference in risks—0.05 – 0.10 = –0.05.
That is, there is a 5 per 100 (5 percent) reduction in the risk of dying if you are treated with the new drug compared with the old. You will see this called absolute risk reduction, or risk difference as well.

\[
\text{Absolute Risk Difference (reduction)} = \text{risk reduction with Drug A} - \text{risk reduction with Drug B}
\]

But not all patients who were treated with either the new drug or the old for the five-year period died (or lived)—if the benefit from these treatments is preventing death, we actually had to treat quite a lot of patients to prevent five deaths. This way of thinking about the treatment benefit leads to another metric: the number of patients needed to treat (to prevent one death)—

\[
\frac{1}{\text{absolute risk difference}}, \text{ in this case:}
\frac{1}{0.05} = 20
\]

So the number needed to treat (NNT) here is 20 patients need to be treated for 5 years to prevent 1 death.

\[
\text{Number of Patients NNT (to prevent 1 death)} = \frac{1}{\text{absolute risk difference}}
\]

In the 2007 SPARCL trial, atorvastatin was studied to determine the effects on the incidence of stroke and cardiovascular events. This study showed that the drug was associated with a significant reduction in the number of cardiovascular events. The NNT was determined to be 16 with a range of 12-24.

You may see these results presented other ways. For example—

the relative risk reduction would be 1- relative risk, i.e., 1— 0.5, or 50 percent.

\[
\text{Relative Risk Reduction (RRR)} = 1- \text{relative risk}
\]

A 50 percent reduction in risk sounds far more attractive the 5 percent absolute risk difference! And needless to say, relative risk reductions are fare more frequently quoted in pharmaceutical advertising material than are NNTs or absolute risk differences. In the SPARCL study described above, the RRR was 23 percent for any cardiovascular event occurring in patients taking atorvastatin.

Yet another way is to see results expressed as odds ratios. If you understand gambling, odds ratios are also easy to follow: the odds of an event is the number who have the event divided by the number who do not.
In our example, in the new treatment group this would be 5/95, or 0.0526. For the odds ratio of the new treatment compared to the old, therefore—

\[
\frac{5}{95} = 0.0526 = 0.474 \\
\frac{10}{90} = 0.111
\]

The odds ratio is not quite the same as the relative risk, but close. However, interpreting odds ratios is not straightforward. For most purposes think of them like a relative risk, but the results will not always be identical, and the more common an event is, the less similar the two metrics will be.

These calculations are simple and important to do yourself. If authors do not give you the NNT, you should work it out as it gives you an idea of costs and benefits—do you, for example have to pay for treatment for 20 patients for 5 years for 1 to have a benefit? If results are only expressed in relative terms in a study, is that because the events are so uncommon that any absolute benefit is tiny? Even in complicated studies, it is a helpful exercise to do the calculations to get an approximate estimate of the effect of the new treatment compared to the old and see how your approximations compare with the quoted results. Depending on the precise statistical analysis used, they won’t necessarily be exactly the same—but they should at least be in the same order of magnitude.

Table 2 below provides the general formula for the calculations assuming you set up the results in the same way as in the example. If the outcome is a benefit (i.e., deaths prevented), the current convention is to express relative risks as values < 1.0; if the outcome is a harm or adverse effect (i.e., deaths caused), the convention is to express the value as > 1.0. As it is easy to confuse the direction, it is important that you always check what the treatment group is and what the control group is for each calculation.
### Table 2. Formulas Commonly Used to Assess Treatment Effect Size Compared to Control

<table>
<thead>
<tr>
<th>Group or Parameter</th>
<th>Number with the Event</th>
<th>Number without the Event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Control group</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Experimental event rate</td>
<td></td>
<td>a/a + b</td>
<td>c/c + d</td>
</tr>
<tr>
<td>Control event rate</td>
<td></td>
<td>a/(a+b)/ c / (c+d)</td>
<td>1-([a/(a+b)/ c / (c+d)]</td>
</tr>
<tr>
<td>Relative risk (experiment/control)</td>
<td></td>
<td>(a/(a+b) - (c/c+d))</td>
<td>1/[(a/(a+b) - (c/(c+d)))]</td>
</tr>
<tr>
<td>Absolute risk difference (experiment—control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number needed to treat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio(treatment/control)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each of these metrics is a way of expressing the point estimate for the size of the effect of the treatment compared to the control group. Equally important is to have an estimate of the 95 percent confidence interval, which can be considered to be the plausible possible range of the results. That is, if the same study were repeated 100 times in different samples of patients, the 95 percent confidence interval would include the true mean point estimate 95 times out of 100.

For those of you who are enthusiasts, the 95 percent confidence interval for the difference between two proportions is as follows—

\[
95\% \text{ CI} = +/- (1.96 \times \text{Standard Error of the Difference})
\]

Where the SED is:

\[
SE_{\text{diff}} = \sqrt{\frac{P_1(1-P_1)}{n_1} + \frac{P_2(1-P_2)}{n_2}}
\]

And \( P \) is probability in group, \( n \) is number in group, subscript indicates group 1 or 2.

The point of considering a confidence interval is that if the metric is the relative risk and the 95 percent CI includes 1.0, then any difference between treatments is probably due to chance (i.e., the \( p \) value would be > 0.05). Similarly, if the metric is the absolute difference and the 95 percent include 0.0, there is no real difference between treatments. However, the upper and lower limits of the confidence interval will give an indication of what the maximum and minimum differences might be and therefore a clinical judgment can be made about the importance of the difference if it exists. See figure 4 for an example—

**What are the Standard Statistical Tests?**

For the clinician and DTC, there are about half a dozen statistical methods that are worth understanding. For purposes of this training, we will list and define (Table 3) the important statistical tests used in drug studies. Participants are referred to the further readings section to obtain more information.
Table 3. Statistical Tests Commonly Used

<table>
<thead>
<tr>
<th>Statistical Test</th>
<th>Use</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Two sample t test</td>
<td>Compares the results for a single measurement of a variable in 2 groups of patients</td>
<td>Girls’ height at age 10 with boys’ height at age 10</td>
</tr>
<tr>
<td>(2) Mann-Whitney U test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Paired t test</td>
<td>Compares the results of two measurements in the same group</td>
<td>Weight before and after feeding in 10-day-old infants</td>
</tr>
<tr>
<td>(2) Wilcoxon matched paired test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1- or 2-way analysis of variance:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Fisher ANOVA</td>
<td>Compares the results of multiple measurements in a group</td>
<td>Repeated measurements of BP over time</td>
</tr>
<tr>
<td>(2) Kruskal-Wallis ANOVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Pearsons correlation coefficient</td>
<td>Assesses the strength of association between one or more factors and another</td>
<td></td>
</tr>
<tr>
<td>(2) Spearmans correlation coefficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression modeling (in a variety of forms)</td>
<td>Describes the numerical relationship between one or more factors and another</td>
<td></td>
</tr>
</tbody>
</table>

Of those tests mentioned, the first (1) in each pair is a parametric test and the second (2) is its nonparametric equivalent. Nonparametric tests (or distribution-free) should be used when one cannot assume that the data for the variable is normally distributed. Nonparametric tests have less power than the appropriate parametric test, but are stronger when the assumptions used for parametric tests are not satisfied.

All of the tests can be used to provide a p value, which, as noted above, is an indicator of whether a result is likely to be due to the play of chance.

In papers published in current journals, the additional method that is used in survival analysis, usually presented graphically as shown in figure 3. This type of analysis will be presented with a hazard ratio (usually derived from Cox’s proportional hazard model) which can be interpreted in a similar way to relative risks.
A useful rule of thumb is that if a paper uses a method that doesn’t seem to be one of the standard ones, have the authors explained why?

Finally, a very useful list of “errors” to remember when assessing the statistics and results in any study, thanks to Trisha Greenhalgh, is shown in box 3.
Box 3. Ten Ways to Cheat on Statistical Tests When Writing Up Results

1. Throw all your data into a computer and report as significant any relation where $P < 0.05$.
2. If baseline differences between the groups favor the intervention group, remember not to adjust for them.
3. Do not test your data to see if they are normally distributed. If you do, you might get stuck with non-parametric tests, which aren't as much fun.
4. Ignore all withdrawals (drop outs) and non-responders, so the analysis only concerns subjects who fully complied with treatment.
5. Always assume that you can plot one set of data against another and calculate an "r value" (Pearson correlation coefficient), and assume that a "significant" r value proves causation.
6. If outliers (points which lay a long way from the others on your graph) are messing up your calculations, just rub them out. But if outliers are helping your case, even if they seem to be spurious results, leave them in.
7. If the confidence intervals of your result overlap zero difference between the groups, leave them out of your report. Better still, mention them briefly in the text but don't draw them in on the graph—and ignore them when drawing your conclusions.
8. If the difference between two groups becomes significant four and a half months into a six month trial, stop the trial and start writing up. Alternatively, if at six months the results are "nearly significant," extend the trial for another three weeks.
9. If your results prove uninteresting, ask the computer to go back and see if any particular subgroups behaved differently. You might find that your intervention worked after all in Chinese women aged 52-61.
10. If analyzing your data the way you plan to does not give the result you wanted, run the figures through a selection of other tests until you get the result you want.


Summary Statement on Single Trials

Critical review of a single trial takes skill, time, and resources, although the skills can be acquired with practice. Even if you only have a few trials for each drug that you are considering, you can expect your DTC to need technical support in critical appraisal. It is not enough just to be able to “trash” a trial—in the end, a committee still has to make a judgment based on the best available information, even if this is a poor quality study.

So ideally you will be able to access more than one trial in relation to each drug, and it is better still there if there is a systematic review.

Systematic Reviews and Meta-Analysis

A systematic review is an overview of individual or primary studies that contains an explicit statement of objectives, materials, and methods, and has been conducted according to explicit and reproducible methodology. They should be distinguished from traditional, or narrative reviews, which are usually written by an author to prove or disprove a particular point and are
therefore likely to be more selective in the studies for citing or inclusion. The advantages of systematic reviews are—

- The use of explicit methods limits bias in identifying and rejecting studies.
- The conclusions are generally more reliable and accurate because of the methods that are used.
- Large amounts of information can be assimilated quickly by health care providers, researchers, and policymakers.
- Results of different studies can be formally compared to establish the generalizability of findings and consistency of results.
- Reasons for heterogeneity (inconsistency in results across studies) can be identified and new hypotheses generated about particular subgroups.
- Where appropriate, results of individual studies can be statistically combined using meta-analysis to provide a single summary estimate of the effect of an intervention.

A major source of a large number of systematic reviews is the Cochrane Library, which contains over 2,500 complete reviews on a wide variety of topics (see: http://www.mrw.interscience.wiley.com/Cochrane) and these are added to every three months. These reviews are also regularly updated to incorporate new evidence as it becomes available.

To fully understand and interpret a systematic review, there are some technical points to consider. These include—

- How the trials included in the systematic review were found, and the potential for publication bias: search strategies and inclusion criteria
- The use of meta-analysis
- The use of sensitivity analysis in interpreting the results
- Interpreting inconsistent results (heterogeneity)

**Search Strategies and Inclusion Criteria**

Any systematic review should include a description of the criteria used by the authors to select studies to include in the review and a description of how they went about finding the studies. This should include not only the definition of the interventions and population in the studies, but whether studies in all languages were included, and also whether unpublished studies were sought for and added to the list. It is well established that negative studies do not get published as often as positive ones, and thus the assessment of the efficacy of an intervention based only on published trials can sometimes be unduly positive.
How the authors went about finding the studies should also be described. There are many electronic databases that index medical studies but searching only the electronic sources such as PubMed can still result in important studies being missed. It is important that authors of a systematic review use multiple strategies to find all the relevant trials, including contacting authors, and if relevant, pharmaceutical manufacturers.

Although systematic reviews have generally focused on pulling together only RCTs, there is increasing interest in systematic reviews of other study types. This is particularly important when assessing the safety of a product, as RCTs may not be sufficient to evaluate adverse effects. However, the same principles should apply to systematic reviews of non-randomized studies: authors should specify in advance what types of studies will be included and how they will find them.

The Use of Systematic Reviews and Meta-Analysis

The term meta-analysis is often used interchangeably with systematic review, but the two should not be confused. Meta-analysis refers to the statistical techniques used to combine the results of clinical trials into a single estimate of effect. It is best thought of as a weighted average effect, with larger trials counting more than smaller ones. Meta-analysis can be used to calculate pooled or summary estimates for all the metrics described above (relative risk, risk difference, and so forth). There are also ways of combining the results of trials that report only continuous outcomes (means, medians, and so forth) but these are more complex and difficult to interpret. Not all systematic reviews can (or should) include a meta-analysis. If the trials appear to be in significantly different populations, of different design, or have different interventions, it may not be clinically sensible to try to combine them.

Meta-analysis results should generally be presented graphically as well as in tables. The standard presentation is the forest plot (figure 4). Each dot represents the results for a single trial with the 95 percent confidence interval and the size of the dot is proportional to the number of subjects in the trial. The summary estimate is the diamond at the bottom of the graph, with the middle of the diamond as the point estimate and the rest of it representing the 95 percent CI. In this example, the summary estimate is the odds ratio for the risk of cancer in patients treated with statins compared with those not treated with statins, and as it is 1.02, with a confidence interval of 0.97 to 1.07, we can be reasonably confident that there is no relationship.
The results of a meta-analysis can be very sensitive to the inclusion and exclusion of trials. For example, if the analysis shown in figure 4 for some reason exclude the HPS and LIPID trials, the pooled estimate would be likely to be quite different. Sometimes it is important for authors to carry out the analyses including and excluding trials—these are called sensitivity analyses. They can be useful tools to understand inconsistent trial results, but should again be specified beforehand.

Interpreting Inconsistent Results (Heterogeneity)

In the language of meta-analysis, homogeneity means that the results of each trial are mathematically compatible with each other. It can be assessed from the forest plot of a meta-analysis: if the confidence limits of all the trials overlap, the trials are probably homogeneous, but if they do not, statistical heterogeneity exists. This is tested for by the $q$ statistic. The challenge for the reviewer is then to determine why there are differences in the results: is it due to chance, or is it a signal that there are real differences between the trials that lead to the different results, such as duration, design, or population sampled?
**Summary of Systematic Reviews**

Systematic reviews, like all other scientific studies can be good, bad, or indifferent. The key points summarized above will help you assess them. A good systematic review that pulls together the results of all relevant clinical trials is the most robust and reliable evidence we currently have and should be a key part of any DTCs decision and assessment process.

**Use of Evidence in Decision-Making**

It is worthwhile to spend a few minutes considering how best to use evidence in decision making. As noted above, it is not sufficient to be able to “trash a trial”—a DTC, like any other decision making group still has to decide what to do. The following approach to using evidence in making treatment recommendations tries to summarize all of the aspects of assessing studies as well as taking into account uncertainty, values, and costs. It has been developed over the past five years by an international group and is gaining increasing acceptance from guidelines groups and other who make treatment recommendations. See also Annex 2 for a checklist to detect common problems encountered in articles.

- First of all, what is the clinical question in terms of patient population, intervention, comparator, and outcome?

- What are the critical outcomes for the intervention? These may not necessarily be measured in the trials.

- For these critical outcomes, what type of evidence do you have? Ideally a systematic review, but this will not always be the case.

- What is the quality of the evidence that you have, including the assessment of study design, concealment of allocation, randomization method, blinding, and completeness of follow-up?

- Is the evidence consistent? Do all the studies generally give the same results? If not, is there a reason for the differences?

- Is the evidence directly related to your setting? Is the comparator relevant, is the intervention the same as the one you are interested in, is the setting of the studies similar? If not, what impact is it likely to have on the overall estimate of effect?

- What is the size of the effect? What is the 95 percent CI? Does it include or exclude clinically important differences?

- What are the harms?

- What are the likely trade-offs between benefit and harm?
What are the costs?

Are there local values and preferences that need to be considered?

Then, taking all of this into account, would you recommend that the intervention should be adopted or not?

Good luck and happy appraising.

We will now work through some practical examples to put all of the theory into practice.

**Activity 1. Comparing Antimicrobial Medicines for Pneumonia**

For this activity, assume your DTC is considering the formulary addition of a new antimicrobial drug for treating lower respiratory tract infections in children. The drug study abstract you have just read concludes that this drug’s efficacy is equal to a combination of antibiotics in treating pneumonia in hospitalized children.

This study looked at 35 children in the treatment group and 43 in the control group. The setting was a large university hospital. This was an open label study, and children receiving a new antimicrobial were compared with other children in the hospital who were receiving different antibiotic combination regimens to treat pneumonia. Patients were chosen to receive this antibiotic by the physician depending on the severity of the pneumonia. The drug requested for the formulary was typically given to children with less severe pneumonia (based on the judgment of the physician) while the combination drug therapy was reserved for children who appeared to be sicker and at higher risk.

Results showed that the study drug was equally effective as a combination of antibiotics and was less costly. There was no difference in the incidence of adverse drug reactions. The manufacturer of the drug sponsored the study.

You are especially interested in such a drug since it is less costly and the study shows that it is effective. Safety information is limited at the early stages of its marketing.

- How would you describe the study design? Is it valid?
- What are the controls in the study?
- How are patients randomized?
- What kinds of bias can be introduced in this type of study?
- Are the results of this study usable in your country?
**Activity 2. Interpreting the Data: The Helsinki Heart Study**

The Helsinki Heart Study identified treatment modalities for elevated lipoproteins through the use of gemfibrozil. Subjects: 4,081 asymptomatic men aged 40–55 with dyslipidemia (total cholesterol minus high-density lipoprotein > 5.2 mmole/liter)

Treatment: gemfibrozil 600 mg twice daily (2,051 men) or matched placebo (2,030 men) in a five-year randomized double-blind study

Results: number of events (fatal, nonfatal myocardial infarction, or cardiac death)

- Gemfibrozil—56 events
- Placebo—84 events

Please calculate the following—

- Event rate for placebo group (%):
- Event rate for active drug group (%):
- Relative risk:
- Relative risk reduction (%):
- Absolute risk reduction (%):
- NNT for five years to prevent one event:

**Activity 3. Critically Evaluating an Article**

One or more articles will be distributed in class. You should work in groups to evaluate the one assigned to you and present your findings in class.

**Activity 4. Interpreting the Data: A Medicine Trial to Compare Artesunate with Mefloquine to Treat Malaria**


**Box 4. Exercise: Managing Malaria**

You are working for the Department of Communicable Diseases. In your country, as in many others, one of the major health problems is malaria. As is the case in other settings, resistance to standard treatment is becoming a significant problem and you are therefore trying to decide what alternative treatments should be included in your standard treatment guidelines. You are aware that artesunate is a relatively new drug that may offer some advantages in the treatment of Falciparum malaria. You have been asked to present a summary of the clinical trial evidence and an assessment of the potential cost-effectiveness of using artesunate compared to mefloquine. Your librarian has identified a possibly useful study from Thailand for you to use as the basis for your assessment.
Complete the following questions.

- What type of study is this? What are the key study design characteristics? Does the study design allow you to address clinical efficacy and potential cost-effectiveness? Is the study relevant to the question that you have been asked to address?

- Were patients, those administering treatment, and those assessing outcomes blinded to the patients’ treatment allocation? Which patients were included in the analyses—all of those randomized? Only those who completed the trials? Are there any baseline differences between the treatment groups?

- How reliable or valid do you think these studies are? What are the reasons for your answer?

Fill in the grid below. Are the study populations similar to those in your country?

### Dosage Regimen and Baseline Characteristics in Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Looareesuwan et al. 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Artesunate N=</td>
</tr>
<tr>
<td>Dosage Regimen</td>
<td></td>
</tr>
<tr>
<td>Proportion male [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Age [mean (standard deviation)]</td>
<td></td>
</tr>
<tr>
<td>Parasite count [Mean(range)]</td>
<td></td>
</tr>
</tbody>
</table>

- What are the outcomes that are presented in the trial?

- Are they relevant to the question that you are trying to answer?

- Are the outcome measures surrogate measures, and if so, has the surrogate been validated?

To help in your interpretation of these studies, we have summarized some of the results from each of them. However, you will still have to review the “Methods” section in each study to confirm exactly how each outcome was measured.

The following grid is the comparison of artesunate and mefloquine (from Looareesuwan et al., 1992). For the moment, we will ignore the combination treatment. Total numbers are the number of patients randomized to each treatment group, and where possible, the results for the “intention to treat” analyses have been presented.
### Efficacy results from Looareesuwan et al. (1992)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Artesunate (N = 42)</th>
<th>Mefloquine (N = 43)</th>
<th>Difference in means (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever clearance time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Mean (standard deviation)]</td>
<td>35.1 (23.4)</td>
<td>69.7 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Parasite clearance time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Mean (standard deviation)]</td>
<td>35.9 (10.1)</td>
<td>63.5 (25.5)</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Artesunate (N = 42)</td>
<td>Mefloquine (N = 43)</td>
<td>Relative risk (95% CI)</td>
</tr>
<tr>
<td>Patients cured at 28 days [n (%)]</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Patients completing 28 days follow-up [n (%)]</td>
<td>40</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

- How have the outcomes been expressed? Based on the data in the grid, how would you determine whether there is a difference in the effects of the treatments, and what the size of the difference is?
- Fill in the gaps in the table (the columns for difference in means, relative risk, risk difference, and 95 percent CI).
- What is the size of the effect of artesunate compared with mefloquine treatment? What is the plausible range of results?
- For each of the outcomes: is the size of the effect clinically important? Are all of the values included in the 95 percent CI also clinically important?
- In terms of effectiveness, do you think this trial provides evidence of superiority of artesunate compared with mefloquine?
Annex 1. Glossary

**Allocation**—The process of assigning patients to treatment groups.

**Bias**—Anything that leads to deviation of the results from the truth or processes leading to such deviation. This deviation can be either conscious or subconscious, but it allows for systematic error to enter a clinical trial and leads to an incorrect estimate of the outcome of interest. A bias can be a prejudice or a specific opinion favoring an issue before there is adequate information to support the position. Different types of bias occur in all studies and careful design, blinding, and randomization will effectively limit bias.

**Blinding**—An experiment is “double-blinded” if neither the investigator nor the patient is aware of the treatment a patient is receiving. The goal of blinding is to try to exclude investigator or participant biases that may influence outcomes or the reporting of outcome variables. To achieve blinding, a common practice is to administer identical appearing (and tasting) medication at identical times to all subjects.

*Observer-Blind*—The person measuring the outcomes in a study is not told what treatment patients have been received.

*Double-Blind*—Neither the observer nor the patient in a trial knows what treatment the patients received.

**Cohort study**—Patients are grouped according to their exposure or lack of exposure to a particular factor (e.g., a therapy). Outcomes over time then are compared in the different groups. Most cohort studies are prospective, but cohort analyses also can be performed retrospectively.

**Confidence Intervals**—The CI indicates the range within which the true study results lie. By convention 95 percent CIs are used and indicate that there is a 95 percent chance that the true results lies within the observed or estimated range. The larger the sample size, the narrower the CI of an observed value (e.g., mean reduction in blood pressure or percent of patients with pain relief). A smaller CI means that we can be more confident that the results of a study are indeed reliable and not due to chance alone. Confidence intervals are useful in determining what values could be expected for the population in general as opposed to those found with the smaller study sample.

**Confounding factor or variable**—A variable that can cause or prevent the outcome of interest, is not an intermediate variable and is associated with the factor under investigation. Confounders can also be described as an alternative explanation for a result in the study.

**Control groups**—Comparative trials utilize control groups as a reference standard against which to compare outcomes observed in the treatment (intervention) under investigation. Examples of control groups include placebo, alternative treatment, and historical. Control groups should closely resemble the group receiving experimental therapy in baseline demographic and clinical characteristics.
Descriptive studies—Include case reports and clinical series that present outcomes in treated patients. Benefits of treatment or adverse drug reactions may be reported.

Intention-to-treat population—The total number of patients assigned to receive a particular treatment, irrespective of whether they actually received it or not.

Null Hypothesis—All drug trials test a hypothesis that says Drug A is superior or safer or different due to some other parameter as compared to Drug B or no drug (placebo). An opposing hypothesis, the null hypothesis, states that there is no difference between Drug A and Drug B or placebo and the drug trial must seek to substantiate or refute it. Formulation of the null hypothesis is a vital step in testing statistical significance. Having formulated such a hypothesis, one can establish the probability of observing outcomes more different from the prediction of the null hypothesis, if the null hypothesis is true. That probability is what is commonly called the "significance level" of the results. That is, in our drug trial, we may predict that Drug A will produce a greater effect on our outcome of interest as compared to Drug B — this is our alternative hypothesis. We then consider how often we would expect to observe our experimental results (outcomes), or results even more extreme, if we were to take many samples from a population where there was no effect (i.e., we test against our null hypothesis). If we find that this happens rarely (up to, say, 5 percent of the time), we can conclude that our results support our experimental prediction — we accept our alternative hypothesis that drug A is different from Drug B. Even so any significant difference observed between drugs may be a result of error inherent in the study and not due to any differences of outcome due to the drugs themselves.

Observational studies—Studies where the investigators do not have control over what happens to patients or subjects. They are used to detect the cause of health problems or to describe consequences of treatment. Examples include case control, cohort, and cross-sectional studies. These studies may use comparison groups but do not control for the effects of variables as well as randomized controlled trials. This type of study can provide useful information about drug safety, but not usually on efficacy.

The power of a study—Indicates the likelihood of a hypothesized result being observed and is dependent on sample size. A value of 80 percent is taken by convention to be the minimum and indicates that there is an 80 percent 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.

P Value—Expresses the probability that any results observed in a study are real and 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 percent chance of observing a result which does not exist in the population. This means that there is a 95 percent chance that any difference observed, for example, between the drug of interest and the comparator drug, is a true difference in the population.

Randomization—The process of assigning patients to treatment groups by chance. True random selection occurs when patients have an equal chance of receiving standard or experimental therapy, assuming equal numbers of patients are to be assigned to each group.

Randomized comparative trial—Patients being studied are allocated by chance to either the new intervention that is being tested, or the alternative comparative treatment. This is the “gold
standard” as it minimizes bias and control for confounding variables. However, randomized controlled trials are expensive and time-consuming and can raise ethical concerns about the treatment strategies. Therefore, some investigators may elect not to use this type of study design.

**Sampling**—The term used to describe the selection of patients for a clinical study. Many clinical studies aim to obtain a cross-section of the population, one that represents different ages, ethnicity, regions of the country, life styles, and health conditions. In other studies, the sampling may be more targeted and look at a particular subpopulation or group.

**Statistical Power**—The probability that the test will reject a false null hypothesis. In other words, statistical power is the likelihood that the experiment will detect a treatment effect that truly exists in the population. A power of 80 to 90 percent is considered acceptable in most clinical studies and this means that 5 out of 5 to 9 out of 10 trials will detect a difference that truly exists. A type I error is where a study detects a difference that does not truly exist in the population, that is, a false positive result (or a wrong rejection of the null hypothesis. A type II error is where a study does not detect a difference that truly exists, that is, a false negative result (or a wrong acceptance of the null hypothesis. As power increases, the chances of a Type II error decrease, and vice versa. A power of 80 to 90 percent means that 1 in 5 to 1 in 10 trials will fail to detect a difference that truly exists in the population.
Annex 2. Checklist to Detect Common Problems Encountered in Articles


<table>
<thead>
<tr>
<th>Checklist</th>
<th>Potential Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
<td></td>
</tr>
<tr>
<td>Are the objectives stated in the abstract, introduction or methods?</td>
<td>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.</td>
</tr>
<tr>
<td>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?</td>
<td>Clinically unimportant outcomes may be used.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Was a randomized control trial (RCT) done?</td>
<td>The study design may be insufficient to be able to ascribe observed differences to the new drug being tested.</td>
</tr>
<tr>
<td>• Best design for efficacy</td>
<td></td>
</tr>
<tr>
<td>Was a case control study done?</td>
<td></td>
</tr>
<tr>
<td>• Commonest design for safety</td>
<td></td>
</tr>
<tr>
<td>Was the study blinded? If not, is this explicitly discussed? And are the confounders accounted for?</td>
<td>Study participants or investigators are not blinded leading to possible bias in interpreting the results.</td>
</tr>
<tr>
<td>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?</td>
<td>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.</td>
</tr>
<tr>
<td>Was the sample size of patients sufficient to detect significant differences in outcomes between intervention and control groups?</td>
<td>The number of patients may be too small to ensure any differences are not due to chance.</td>
</tr>
<tr>
<td>• Were the inclusion and exclusion criteria of patients specified?</td>
<td>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.</td>
</tr>
<tr>
<td>• Was the assignment of patients randomized?</td>
<td></td>
</tr>
<tr>
<td>• Were the control subjects appropriate?</td>
<td></td>
</tr>
<tr>
<td>• Is the drop-out rate of patients in the intervention and control groups reported?</td>
<td>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.</td>
</tr>
<tr>
<td>• Were the rates the same? If not, is any explanation given for the different rates?</td>
<td></td>
</tr>
<tr>
<td>How many dose regimes were compared for each drug? Were they equivalent?</td>
<td>Different drugs may be compared using fixed non-equivalent doses; the comparator drug may be under-dosed.</td>
</tr>
<tr>
<td><strong>Review articles and meta-analysis</strong> (analysis across different RCT studies)</td>
<td>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.</td>
</tr>
<tr>
<td>• What criteria were used to find the articles?</td>
<td></td>
</tr>
<tr>
<td>• How was the search done?</td>
<td></td>
</tr>
<tr>
<td>• Which databases were used and were</td>
<td></td>
</tr>
<tr>
<td>Checklist</td>
<td>Potential Problems</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>unpublished articles included?</td>
<td></td>
</tr>
<tr>
<td>• Is there a description of how individual studies were appraised, and, if relevant, meta-analysis done?</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
</tr>
<tr>
<td><strong>Economic articles</strong></td>
<td></td>
</tr>
<tr>
<td>• Are all the costs associated with drug treatment, including good and bad outcomes, described? (not just prices)</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<tr>
<td>• Has discounting been used to reflect the costs of any future benefits or consequences in present day values?</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<tr>
<td><strong>Results</strong></td>
<td>The presentation and analysis of data may be misleading.</td>
</tr>
<tr>
<td>• What measures of outcome were used?</td>
<td>Differing efficacy can only be assessed by using established measures, for example, relative or absolute risk reduction or number of patients needed to treat. Economic evaluation requires using standard analyses.</td>
</tr>
<tr>
<td>• 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?</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<td>• For economic studies:</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<td>What type of analysis was done? cost minimization? Cost-effectiveness analysis?</td>
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<tr>
<td>Has a sensitivity analysis been done?</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<tr>
<td>Were the differences in clinical outcome between groups large, important and relevant as well statistically significant?</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<tr>
<td>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.</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<tr>
<td><strong>Conclusions</strong></td>
<td>Confounding variables may not have been adequately controlled so that any differences seen are due to the confounders not the new drug.</td>
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<tr>
<td>Were the populations for which conclusions were drawn represented by the subjects in the study?</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
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<tr>
<td>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.</td>
<td><strong>Economic articles</strong> may be biased due to incomplete reporting of all the costs associated with a drug treatment, that is, non-drug costs (e.g., equipment) and outcomes, including negative ones (e.g., side-effects). Different discounting rates for drug costs and future benefits may be used to emphasize a drug’s cost-effectiveness ratio.</td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td>The study may have been funded by a drug company for their own product; often drug companies do not publish negative studies</td>
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<tr>
<td>• Is there a description of how the study was funded?</td>
<td>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.</td>
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<tr>
<td>• What is the reputation of the authors and are their affiliations described?</td>
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<tr>
<td>• Is the study published in a peer-reviewed journal that is listed in Index Medicus, which covers all major reputable journals?</td>
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Drug and Therapeutics Committee
Training Course

Session 4.
Assessing and Managing Medicine Safety
SESSION 4. ASSESSING AND MANAGING MEDICINE SAFETY

Purpose and Content

Session 4 provides participants with basic information about assessing and managing medicine safety issues.

Objectives

After attending this session, participants will be able to—

- Describe the significance of adverse drugs reactions (ADRs)
- Describe the significance of medication and prescribing errors
- Understand the principles of medicine safety evaluation
- Understand the management of spontaneous case reports of ADRs and medication errors
- Understand the process of monitoring, evaluating, and preventing ADRs and adverse drug events.

Preparation and Materials

Read the Participants’ Guide.

Further Reading


Key Definitions

**Adverse drug reaction (ADR)**—The World Health Organization defines an ADR as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.”\(^\text{10}\) In other words, an ADR is harm directly caused by the medicine at normal doses, during normal use. An unexpected ADR refers to a reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or is unexpected from characteristics of the medicine. The term *adverse drug effect* is interchangeable with *adverse drug reaction*.

**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 medicine. Such effect may be either positive or negative. Such effects may be well-known and even expected and may require little or no change in patient management.

**Serious Adverse Effect**—Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability or incapacity, or is life threatening.

**Adverse Drug Event**—Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.

**Causality**—The probability that a particular medicine or substance is responsible for an isolated effect or ADR.

**Signal**—Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being previously unknown or incompletely documented. Usually more than one signal report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

**Prescribing error**—Incorrect medicine ordering by a prescriber.

**Medication error**—Administration of a medicine or dose that differs from the written order.

**Negligence**—Medical decision making or care below accepted standards of practice.

Introduction

Medicines have become one of the most essential components of health care systems worldwide. Medicines save lives. This indisputable fact makes rational selection, procurement, distribution, and rational use of medicines of paramount importance in health care.

Unfortunately, there are often shortcomings in prescribing and taking medicines. One important concern is that of safety. Medicines are produced synthetically or from natural substances, and most will exhibit some form of side effect or adverse reaction. These side effects or adverse reactions may range from relatively mild to, in rare cases, serious and life threatening. Session 4 discusses medicine safety issues, how to assess the true extent of the problem, and how to monitor and prevent medicine-related safety problems.

Adverse Drug Reactions

ADRs are unexpected, unintended, undesirable, or excessive responses to a medicine, and they may be harmful to the patient. By contrast, side effects are known reactions to a medicine and are typically listed in the medicine’s labeling.

The American Society of Health-System Pharmacists\(^\text{11}\) provides another definition of ADR. It describes an ADR as any unexpected, unintended, undesirable, or excessive response to a medicine that—

- Requires discontinuing the medicine (therapeutic or diagnostic)
- Requires changing the pharmaceutical therapy
- Requires modifying the dose (except for minor dosage adjustments)
- Necessitates admission to a hospital
- Prolongs the patient’s stay in a health care facility
- Necessitates supportive treatment
- Significantly complicates diagnosis
- Negatively affects prognosis
- Results in temporary or permanent harm or disability, or in death

ADRs can be classified into six types—

- \textit{Type A reactions} (dose-related)—These reactions are an exaggerated, but otherwise normal pharmacological responses to the effects of the medicines given in therapeutic dose, cause significant morbidity but are rarely severe. The reaction is treated by reducing the dose or withholding the medicine and considering alternative therapy. Examples of such reactions include—
  - Pharmacodynamic (e.g., bronchospasm from beta-blocker administration)
  - Toxic (e.g., deafness from overdosing of aminoglycosides)

• **Type B reactions** (non-dose related)—These reactions are bizarre and unpredictable with no relation to dose or pharmacological action of the medicine and are often allergic in nature. They are uncommon but are often severe and cause high mortality. The reaction is treated by stopping the medicine and avoiding it in the future. Examples of such reactions include—
  o Medicine-induced diseases (e.g., antibiotic-associated colitis)
  o Allergic reactions (e.g., anaphylactic reaction to penicillin administration)
  o Idiosyncratic reactions (e.g., irreversible aplastic anemia caused by chloramphenicol)

• Type C reactions (dose-related and time-related)—These reactions are chronic (long term) and related to cumulative dose. The reaction is treated by reducing the dose or withholding the medicine, which may have to be withheld for a long time. Examples of such a reaction include—
  o Osteoporosis with oral steroids
  o Hypothalamic-pituitary-adrenal axis suppression by corticosteroids

• **Type D reactions** (time related)—These reactions are delayed (i.e., have a lag time) after the use of a drug. They are uncommon but their treatment is often intractable. Examples of such reactions include—
  o Teratogenic effects with anticonvulsants or lisinopril
  o Carcinogenesis
  o Tardive dyskinesia

• **Type E reactions** (withdrawal)—These reactions occur soon after the end of use (i.e., withdrawal) and are uncommon. The reaction is treated by reintroducing the medicine and then withdrawing it slowly. Examples of this reaction include—
  o Withdrawal syndrome with benzodiazepines
  o Opiate withdrawal syndrome
  o Myocardial ischemia after beta-blocker withdrawal

• **Type F reactions** (unexpected failure of efficacy)—These reactions occur when there is a failure of efficacy. Such reactions are common, may be dose-related and are often caused by drug interactions. The reaction is treated by increasing the dose and considering the effects of concomitant therapy. Examples include—
  o Resistance to antimicrobials
  o Inadequate dosage or oral contraceptives, particularly when used with specific enzyme inducers

Adverse reactions as a result of medicine interactions may be manifested in all degrees of severity and type including—

- Reduced absorption of tetracyclines if administered with calcium
- Phenytoin toxicity when administered in conjunction with fluconazole
- Digoxin toxicity when administered with furosemide
ADRs are a serious problem with increasing incidence as more medicines become available and more people become exposed to them. In the United States, a review of prospective studies showed that hospitalized patients in 1994 had 2.2 million ADRs (6.7 percent incidence), which resulted in 106,000 fatalities. These statistics become even more significant considering that they do not include errors of administration, which would only increase the total incidence of morbidity and mortality related to medicine use. The United Kingdom’s National Health Service reports that ADRs resulted in approximately 250,000 admissions each year and cost the health system £466 million (870 million U.S. dollars [USD]) yearly.

Extrapolating these figures to other countries is difficult, but assuming that all countries have a significant problem in terms of ADRs, a subsequent increase in morbidity and mortality as a direct result is reasonable. Most medicines undergo a significant amount of testing and evaluation before marketing to ensure the product is not only effective but also safe. No medicines on the market today are free of side effects or adverse reactions. Many products have an extremely low incidence of side effects, such as cromolyn inhalation products. Others, such as antineoplastic medicines, exhibit extremely high incidence of adverse reactions, many resulting in death. A close monitoring and evaluation of most medicines is necessary to prevent more serious side effects from occurring.

Marketing a new medicine requires many clinical trials to establish efficacy, safety, quality, and cost-benefit. Clinical trials will determine the most common adverse events, those with an occurrence of 1 percent or more during the development of a new medicine. Adverse events that are less common (<1 percent incidence) may not be identified in these premarketing studies and will rely on postmarketing clinical studies and reporting by physicians, pharmacists, and patients for identification of these uncommon events.

Every medicine has a risk-benefit ratio. Depending on the patient’s condition being treated, ancillary problems, age, and many other parameters, the patient can be expected to obtain both a measurable benefit and experience a certain degree of risk. Careful evaluation by the practitioner before use of the medicine is always necessary to obtain the most beneficial effect from the medicine, minimize ADRs, and obtain value for the cost of the product. This evaluation can be accomplished by careful review of the patient’s history, evaluation of current health status, and the avoidance of medicine that may have a higher incidence of ADRs in the patient.

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Premarketing Safety Evaluations

Premarketing testing is extensive for most medicines that are produced in Japan, North America, and Europe. Typically a new medicine would have the following evaluation before being marketed—

- Animal studies
  - Acute and chronic toxicity—Studies are conducted for various periods, from 14 days to over one year in two or more species of test animal
  - Mutagenicity and carcinogenicity—A battery of mutagenicity tests evaluates the potential for genetic problems; testing is performed in at least two animal species for a period of two years; testing is done only if the medicine is intended for chronic use
  - Teratogenicity—Tests are performed on animal species to assess ability to reproduce and have a normal offspring free of birth defects; the ability of the offspring to grow normally and reproduce is also tested extensively

- Human studies (clinical trials)—Study of the effects of medicines on humans under rigorously controlled trials; most clinical trials will assess safety. The average number of clinical trials performed before a medicine is approved is 68; the average number of patients used in these trials is approximately 4,000.
  - Phase I—Single-dose studies, using low doses of the medicine. Subsequently larger doses and multiple sequences are evaluated.
  - Phase II—Efficacy and safety studies. Efficacy is the primary objective of phase II trials, but safety is also continuously monitored and evaluated.
  - Phase III—Evaluations of safety in groups of patients with the disease. Phase III trials may study the effects of the medicine on, for example, the elderly or patients who have ancillary diseases, use other medicines, and have compromised renal and liver function
  - Phase IV—Postmarketing surveillance and clinical trials

Premarketing safety evaluations have two significant drawbacks—

- Under-identification of ADRs—Low-incidence ADRs, those reactions with an incidence less than 1 percent, are frequently not identified.

- Over-identification of ADRs—Many ADRs that are identified in preclinical studies are not proven to be causal, but are still listed in the product literature as potentially causing the ADR. This practice provides some measure of legal protection for the pharmaceutical
company but is misleading to practitioners, because many of these reactions are not definitely proven.

**Postmarketing Surveillance of ADRs**

After medicines have been released on the market, manufacturers are responsible for postmarketing surveillance of these products. Identifying all of the safety-related problems that may exist with a new medicine is not possible during premarketing testing and evaluation.

Medicines released onto the open market will be used not only by more people, but also by older and sicker people, different ethnic groups, pregnant women, and children and will be prescribed in many different dose regimens (not necessarily the correct and approved dose). These circumstances inevitably lead to a potential for more ADRs.

**Spontaneous Reports**

Spontaneous reports are reports of an ADR by a physician, pharmacist, or patient. In many countries these reports are sent to regulatory agencies or the manufacturer of the medicine.

Spontaneous reports have been shown to identify new ADRs more often than any other method. Consequently, this reporting and identification method has held the most significance for manufacturers over the past 10 years. These reports have the advantage of being available immediately as new products are released and throughout the market life of the medicine. A spontaneous report of a reaction describes the reaction that has occurred, but need only have the suspicion that an adverse event may be related to the use of the medicine. All serious reactions (i.e., those that lead to death, hospitalization, significant or permanent disability, or to congenital abnormality or that require medical or surgical intervention) should be reported. Many less serious reactions should also be reported, especially new and unusual reactions.

The greatest limitation of spontaneous reports is that there is significant underreporting of adverse reactions. Another limitation of spontaneous reporting is a high incidence of false positives in the reporting of adverse events. Many practitioners find accurate assessing and determining the causality of an ADR to be difficult, and the incidence of erroneous reports by physicians and pharmacists is high. Patients are also a source for the reporting of an adverse event and the quality of these reports is frequently unreliable.

Multinational pharmaceutical manufacturers employ a worldwide system of collection, aggregation, and evaluation of ADRs. Data are collected by telephone calls, letters, and literature reviews, and through regulatory authorities. The companies report serious ADRs to regulatory organizations on a regular basis.

**Clinical Studies**

Postmarketing clinical studies are frequently done to assess efficacy and safety. The two methods used are randomized control trials and observational studies.
Randomized Controlled Trials

Randomized controlled trials (RCT) are valuable tools for uncovering adverse events in preclinical studies. For postmarketing discovery of events, however, the RCT is frequently disappointing. The elimination of confounding factors is excellent in this setting, but RCTs generally have insufficient power in the trial to discover an event that was not already observed in premarketing studies. RCTs are also expensive and difficult to manage.

Observational Studies

Large databases from national health programs and from large health maintenance organizations (HMOs) in North America and Europe provide valuable information concerning medicine safety. These databases (with millions of entries) are acceptable for providing information in a case-control or cohort study. A case-control study is a study in which patients who already have a certain condition are compared with people who do not. A cohort study identifies two groups of patients: one that is exposed to the study medicine and another that is not treated or receives an alternate form of therapy.

Pharmaceutical manufacturers frequently set up and sponsor large cohort studies to assess safety issues that have arisen after a medicine has come to market. These studies allow for the control of potential confounders, bias, and chance to a greater extent than spontaneous reports or case reports, but still are susceptible to these factors. Cohort studies are helpful in attempting to assign causality when spontaneous reports indicate a potential for a medicine to cause an adverse event. These types of studies can be unsuccessful because the numbers of patients selected will often be insufficient to provide statistical significance for rare ADRs.

Published Case Reports

Published case reports can be found in medical and pharmaceutical journals and describe the occurrence of a significant ADR. These reports can have drawbacks because they may not be well documented and have a long lead-time from the identification of the event to publication in a journal. These reports are also published at the discretion of editors and publishers.

Meta-Analysis of Clinical Studies

Meta-analysis of published studies is another valuable method to obtain information concerning the incidence and prevalence of ADRs. A meta-analysis takes two or more single studies concerning a particular medicine or reaction and combines them to provide more power for the statistical analysis. Individual reports may not have the statistical power to make conclusions concerning an ADR, but combining several reports will provide the appropriate numbers when one study showed only an insignificant effect.

Corrective Action Concerning Newly Identified ADRs

The surveillance systems currently in place inevitably obtain important new information about medicine safety and ADRs. This information is placed in a database and analyzed by
manufacturers or regulatory agencies. When it becomes apparent that a new safety concern has been detected, appropriate action is taken. The response is usually in one of three forms—

- **Letters**—These letters are sent to physicians and pharmacists describing a concern about a particular medicine. The letter may provide specifics about the new safety concern and how it may affect present patients on the medicine and future prescribing. It may be only a warning of possible safety concerns that have been detected and may recommend a continued vigilance in prescribing and dispensing the medicine.

- **Package insert revisions**—When safety concerns become significant, manufacturers must change the label of the product. This action requires changing the official labeling and changing the package insert to reflect the new safety concern. Regulatory officials typically approve the change.

- **Medicine recalls**—Surveillance systems are intended to monitor medicine safety. Manufacturers and regulatory authorities are responsible for monitoring and assessing the postmarketing surveillance reports. When thresholds for acceptable ADR incidence (or for quality issues) are exceeded and the risk of side effects outweighs the benefits, then withdrawing the medicine from the market may be necessary. Medicine recalls can be voluntary or imposed by regulatory authorities. This action is rarely necessary.

**Determining Causality of an ADR**

Causality of an ADR is a critical issue that requires the linking of any adverse event to a medicine or other cause. Manufacturers, drug regulatory agencies, and DTCs must determine causality of isolated ADRs. When a specific symptom occurs following the administration of a medicine, it does not necessarily mean that the medicine is responsible. Numerous other possibilities may be responsible for the adverse event. Conversely, an analyst cannot conclude that, because a particular medicine has not been taken for some time and an adverse event occurs, that the time interval eliminates the medicine as a cause of the event.

The following associations support causation linking a medicine and suspected adverse reaction.¹⁴ (See table 1.)

- Strength of the association
- Consistency of the observed evidence
- Temporality of the relationship
- Dose-response relationship
- Confounding factors

Table 1. Determining the Causality of an ADR

<table>
<thead>
<tr>
<th>Association</th>
<th>Description</th>
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<tbody>
<tr>
<td>Strength of association</td>
<td>If the odds are known and high for an observed event (e.g., gastrointestinal upset with aspirin), then the case is strengthened for causation.</td>
</tr>
<tr>
<td>Consistency of the observed evidence</td>
<td>When a medicine and an ADR have an association that has been demonstrated consistently over years of clinical practice, causality becomes more likely.</td>
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</table>
| Temporality of the relationship    | The closer the relationship of the administration of the medicine and the occurrence of the ADR, the more likely that the medicine may be the actual cause of the reaction.  
This temporality is not always a true indication, however, because some adverse events may occur several days or weeks after the administration of the offending medicine. |
| Dose-response relationship         | Frequently, adverse events occur in relation to the dose being administered. The higher the dose of the medicine, the more likely an ADR is a result of the administered agent. A lower dose has a corresponding decrease in the ADR. 
This relationship is not always true, however, because very low doses of some medicines (e.g., penicillin) can elicit serious anaphylactic responses. |
| Confounding factors                | Minimizing confounding factors is important in determining causality. Confounding factors such as the administration of other medicines, food, and beverages can account for observed events. The existence of concurrent diseases and infections can also cause certain observed effects, so distinguishing them from the suspected medicine is difficult. Environmental factors, such as air pollutants, weather conditions, and exposure to allergens, may also play a role. |

Causality Assessment of Suspected Adverse Reactions

The causality categories described in this section were established by the WHO Uppsala Monitoring Centre, Uppsala, Sweden.

Certain causality is when a clinical event (including laboratory test abnormality) occurs in a plausible time relationship to medicine administration and cannot be explained by concurrent disease or other medicines 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 when a clinical event occurs with a reasonable time sequence to medicine administration, and it is unlikely to be due to any concurrent disease or other medicine administration.

Possible or likely causality is when a clinical event occurs with a reasonable time sequence to medicine administration, but which could be explained by concurrent disease or other medicine administration. Information on medicine withdrawal may be lacking or unclear.

Unlikely causality is when a clinical event, including laboratory test abnormality, occurs with a temporal relationship to medicine administration that makes a causal relationship improbable, and in which other medicines, chemicals, or underlying disease provide plausible explanations.

Implications for the DTC

Monitoring of ADRs by the DTC

DTCs should implement programs that track and report ADRs throughout the health care system. This effort would include a system for monitoring medicines and vaccines. There are several methods to accomplish this end and at minimum the following would be provided—

- Reporting of ADRs (including vaccines) to the DTC on standard forms (see annex 1)
- Analysis of ADR reports to include statistical analysis of prevalence, severity, and trends in the occurrence of ADRs
- Discussion and evaluation of reports by the DTC on a regular schedule (quarterly) and reporting to medical staff
- Reporting to manufacturers and national regulatory authorities of severe, new, or unusual reactions

Monitoring of ADRs should also include the review of the medication error and product quality reporting systems. These reporting and tracking systems are important because product quality and medication errors may have a significant effect on the occurrence of ADRs.

Managing ADRs from Hospitals and Clinics

The DTC should become involved in the processing and analysis of spontaneous case reports arising from patients and medical providers. These spontaneous reports from practitioners may be difficult to interpret and to assign causality. The following are frequent problems that arise with ADRs reported at a hospital or primary care clinic—

- A particular generic medicine causes an ADR, but the brand name product does not.
- A brand name product is alleged to cause more side effects than another branded product.
• An antibiotic suspension causes a reaction, and it is unclear if responsibility lies with the antibiotic or one of the components of the suspension (i.e., dyes or other excipients in the suspension).

• An injectable product causes a reaction, and it is unclear if the causative agent is the active ingredient or is related to a preservative or other agent in the solvent.

• A patient is on several medicines when a new adverse event is reported; assigning causality becomes problematic because any number of the medicines may be the cause.

• The patient has co-morbid conditions that may have a bearing on the medicine and suspected ADR.

The following steps are necessary to evaluate an ADR observed in the hospital or primary care clinic.

1. Evaluate the nature of the event

   • Obtain a detailed history of the patient including current health status, current pharmaceutical therapy, and past medical history. Use an ADR reporting form to organize reporting. (See annex 1.)

   • Identify and document the clinical reaction. Look up suspected medicines and known ADRs in the literature, and match them with the reactions described by the patient.

   • Classify severity of the reaction—
     o Severe—Fatal or life threatening
     o Moderate—Requires antidote, medical procedure, or hospitalization
     o Mild—Obvious symptoms that require only the discontinuation of pharmaceutical therapy
     o Incidental—Mild symptoms; patient given the option to continue or discontinue medication

2. Establish the cause

   • Use the Naranjo algorithm (or other system) for assessing the reaction and establishing the cause. This algorithm will assist the practitioner in determining the probability that an ADR has actually occurred from the suspected medicine. The algorithm asks a number of questions about the adverse event and provides a numerical rating for the importance of each question. The scores for all items are added to give a probability of causality of the adverse event. (See annex 2.)
• Evaluate the quality of the product from the manufacturer to rule out any adverse event occurring from a poor-quality product. This investigation should include the possibility of pharmaceutical counterfeiting and overt contamination of the product.

• Finally, check for a medication error.

3. *Take corrective and follow-up action*

With information obtained through this process, make a definitive decision based upon the facts as presented. Determine if the reaction is an ADR, adverse drug event (including medication error), or a quality defect. All significant ADRs must be recorded on the patient’s medical record. The following actions may be required of the DTC after the evaluation of serious or recurring ADRs at its hospitals and clinics—

• Educate prescribers.

• Change formulary or standard treatment guidelines, if necessary, to obtain a medicine of proven safety.

• Modify patient monitoring procedures.

• Report to national drug authority and the manufacturer, especially with regard to serious reactions, a new ADR, or an unusual manifestation of a known ADR.

After all ADRs, educate and warn patients to reduce the possibility of ADR recurrence.

**Prevention of ADRs and Adverse Drug Events**

Prevention of many serious ADRs is possible and a necessary function of the DTC. Without a prevention program, many ADRs will occur needlessly, producing an increase in morbidity and associated health care cost. Many authorities agree that over 50 percent of ADRs may be preventable. There is a general lack of knowledge concerning ADRs, including the incidence, severity, and impact on health care. Many ADRs are related to the prescribing of an incorrect dose and to administration of a medicine to a patient with a known allergy. The schematic in figure 1 illustrates the factors that contribute to preventable adverse reactions.
Figure 1. Schematic of preventable and unavoidable adverse events.

Preventing an ADR can be enhanced by the practitioner by evaluating the following before prescribing a medicine—

- Is this medicine the correct one for the patient’s clinical condition?
- Are the dose, route, and interval correct?
- 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 chemically similar medicine?
- Is the patient on another medicine (or herbal product) that would cause a significant medicine interaction?
- What is the patient’s compliance with the medication?
- Is the medicine being prescribed a medicine that is at high risk for producing ADRs (e.g., aminoglycosides, digoxin, warfarin, heparin, and antineoplastics)? Special precautions are necessary when using these high-risk medicines.
- Is the medicine being prescribed of high quality (i.e., reputable manufacturer, not expired, no deterioration)?
- Is the medicine being administered correctly (e.g., sterile needle or syringe for injectable medicines or with food for gastrointestinal irritants)?
The following actions by the DTC can help limit the occurrence of ADRs—

- Review ADR reports regularly, and inform the professional staff of the incidence and impact of ADRs in the region.

- Discuss changes in the formulary or standard treatment guidelines for significant or recurring problems with ADRs.

- Educate staff, especially providers, concerning ADRs.
  - In-service education
  - Face-to-face education with providers
  - Medicine information bulletins
  - Reports of collected adverse events

- Identify medicines on the formulary that are high risk and should be monitored closely by physicians and pharmacists. For example—
  - Aminoglycosides
  - Antineoplastics
  - Digoxin
  - Heparin
  - Warfarin

- Identify high-risk patient populations, including pregnant women, breast-feeding women, the elderly, children, and patients with renal or liver dysfunction; close monitoring of these patient populations by physicians and pharmacists will help prevent serious adverse reactions.

- Review medication errors and product quality complaints to ensure they are not contributing to the incidence of ADRs at the hospital.

**Adverse Drug Events**

An adverse drug event is any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment. Adverse drug events include medication errors.

Studies of adverse drug events and errors in medication prescribing and administration have been conducted in developed countries where resources for such studies are available. These studies have shown a substantial problem in terms of patient injury and increased cost of health care. The risk of an adverse drug event has been about 1 to 5 percent in U.S. hospitals, and about one-third of the events were preventable. Preventable adverse drug events added more than four days to the length of stay and more than USD 4,000 to the cost of the hospital admission. Most errors that result in adverse drug events occur at the stage of physician ordering or medicine administration.
A record review of 15,000 inpatients in the United States in 1992 revealed that there were 2.9 percent adverse events (30 percent due negligence) and 35 percent adverse drug events due to negligence. Primary medicines involved were—

- Antibiotics—25 percent
- Cardiovascular medicines—17 percent
- Analgesics—9 percent
- Anticoagulants—9 percent

Types of medicine use errors include—

- Wrong medicine prescribed—21 percent
- Prescribed despite known allergy—6 percent
- Incorrect frequency—5 percent
- Wrong dose—8 percent
- Missed dose—5 percent
- Medicine interaction—3 percent

A study of adverse drug events at two major tertiary care hospitals in Boston (Massachusetts General Hospital and Brigham and Women’s Hospital) in 1993 found 247 adverse drug events in 4,031 admissions. Seventy (28 percent) of the adverse events were considered preventable. Overall, the risk of an adverse drug event was about 6.1 percent, and the rate was highest among patients in the medical intensive care unit (19.4 episodes per 1,000 patient days). An analysis was conducted of the 70 adverse drug events due to error and an additional 194 potential adverse drug events due to error (i.e., administration or near-administration of an incorrect medicine without evident harm). The 264 preventable events were attributed to 334 errors. Most errors occurred in the physician ordering (39 percent) and nurse administration (38 percent) stages. The remainder were nearly equally divided between transcription (copying or dictating of medication orders) (12 percent) and pharmacy dispensing (11 percent). Although there were almost as many errors in the administration stage as in ordering, nurses were the ones most likely to intercept errors, especially those made by physicians. On further analysis, the cost of ADEs showed the following—

- 247 adverse drug events were estimated to have—
  - Extended hospitalization by 2.2 days
  - Increased cost of USD 3,244

---


• 70 adverse drug events due to errors were estimated to have—
  o Extended hospitalization by 4.6 days
  o Increased cost of 5,857 U.S. dollars\(^{17}\)

In a study of pediatric inpatients, 10,778 medication orders were reviewed and 616 contained errors. Of these, 120 (19.5 percent) were classified as potentially harmful, including 115 potential adverse drug events (18.7 percent) and five preventable adverse drug events (0.8 percent). Most errors occurred at the medicine ordering or prescribing stage (74 percent). Transcribing (5.8 percent), dispensing (1 percent), administration (12.8 percent), and monitoring (0.5 percent) accounted for the other reported errors.\(^{18}\)

The magnitude and causes of the problem of adverse drug events in developing countries are not known. To characterize the problem, it is desirable that individual hospitals establish reporting and monitoring systems. Furthermore, DTCs must take the lead role in developing and disseminating best practice recommendations in each hospital. Important interventions are to provide oversight of physician ordering, especially in intensive care units; to simplify, standardize, and rationalize hospital systems involved in medicine formulation and administration; and to promote adequate staffing so that errors caused by undue haste or fatigue can be avoided.

### Prevention of Medication Errors

Medication errors are common events in hospitals and primary care clinics. Medication errors consist of the administration of medicine or dose that differs from written order and includes—

- Medicine prescribed but not given
- Administration of a medicine not prescribed
- Medicine given to the wrong patient
- Wrong medicine or IV fluid administered
- Wrong dose or strength given
- Wrong dosage form given
- Medicine given for wrong duration
- Wrong preparation of a dose (e.g., incorrect dilution)
- Incorrect administration technique (e.g., unsterile injection)
- Medicine given to a patient with known allergy
- Wrong route of administration used
- Wrong time or frequency of administration

---


There are many causes of medication errors but are generally attributed to the following three factors—

- **Human factors**
  - Heavy staff workload and fatigue
  - Inexperience, lack of training, poor handwriting, and oral orders

- **Workplace factors**
  - Poor lighting, noise, interruptions, excessive workload

- **Pharmaceutical factors**
  - Excessive prescribing
  - Confusing medicine nomenclature, packaging, or labeling
  - Increased number or quantity of medicines per patient
  - Frequency and complexity of calculations needed to prescribe, dispense, or administer a medicine
  - Lack of effective policies and procedures

Two broad interventions to reduce medication errors are (a) improve physician prescribing, and (b) correct systems flaws that predispose to errors. Ideally, educational programs for physicians can be developed with a focus on the most common prescribing errors. These errors, however, involve deficiencies in diverse areas, including knowledge of medicine indications and doses, attention to renal and hepatic function, awareness of medicine interactions, and willingness to routinely check allergy history. A more practical alternative has been to assign pharmacists to monitor medication orders written by physicians.

Specific interventions that are practical, at least in tertiary care hospitals, include the following—

- Establish a consensus group of physicians, pharmacists, and nurses to review current medicine prescribing and administration practices and select best practices.

- Introduce a system to identify and record information about medication errors. To encourage reporting, staff should not fear punishment; the focus should be on system redesign rather than blame.

- Where feasible, institute pharmacy-based admixture of IV fluids. If ward personnel must perform IV admixture, there should be clear written procedures and skills certification of the personnel.

- Develop special procedures for high-risk drugs, such as insulin, heparin, narcotics, theophylline, and aminoglycosides. These procedures should include written guidelines, checklists, and educational materials.
• Require legible handwriting by ordering physicians. Pharmacists and nurses should be instructed to call the prescriber rather than try to interpret illegible orders. Require complete spelling of a medicine’s name.

• Use a standardized designation for doses (i.e., milligrams = mg, micrograms = mcg, and grams = g; use the word “units” rather than “U”; and use a leading zero for values less than 1 but not a trailing zero after a decimal, e.g., write 0.2 mg or 2 mg instead of .2 mg or 2.0 mg).

• Write the route of administration on all orders.

• Write out directions completely. Write “daily” instead of “QD” and “every other day” instead of “QOD.”

• Limit the use of oral or telephone orders to emergency situations, and require that the order be read back to the prescriber.

• When preparing to administer a medication, confirm the identity of the patient by reading the patient’s wristband and talking to the patient or family member.

• To minimize the likelihood that a dose will be missed, standardize administration times and develop a policy to provide doses when a patient is off the floor.

• Analyze medicine names as new products are added to the formulary. For look-alike and sound-alike names, establish a policy requiring that prescribers write both brand and generic name.

• Use pharmacy staff effectively to monitor and manage medicine use and distribution.

Activities

For the activities in this session, the participants will break into groups of five or six individuals. A leader will be selected who will facilitate the discussion within the group. Active discussion within the groups is encouraged.

Activity 1. Penicillin Anaphylaxis Reported

A DTC in Panama served 11 clinics and a hospital. Recently a different brand of procaine penicillin had been purchased and distributed. Shortly after introduction of the new penicillin product, one clinic reported to the DTC that they had experienced an unusually high number of adverse events associated with intramuscular penicillin injections within a short period. The nursing staff became alarmed, refused to use the product that had been distributed, and asked the clinic director to replace the suspect product with an equivalent product from another supplier. They described the adverse event 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
the patients diphenhydramine IV or IM for a suspected anaphylactic reaction to penicillin. Patients would recover 10 to 15 minutes later and would leave the clinic without further assistance.

- How would you analyze this situation? What investigations would you carry out?
- What would you recommend to management regarding the procurement of an alternative or equivalent product?
- What would you communicate to the nursing staff and physicians?

**Activity 2. Acute Respiratory Infection in a Two-Year-Old Patient**

A two-year-old patient and mother present at the clinic on May 19, 1999. The child has a 48-hour history of fever, irritability, cough, and altered consciousness. Questioning of the mother reveals the following—

- 5/14/99—child was administered DPT and oral polio vaccine.
- 5/15/99—child was seen with mild upper respiratory tract infection symptoms and treated with amoxicillin and cough syrup.
- 5/17/99—child experienced the onset of fever, irritability, altered consciousness.
- 5/18/99—child had been seen at the health center and diagnosed with acute respiratory infection and treated with co-trimoxazole and paracetamol.

Consider the following—

- What is the possibility of the patient having an ADR in addition to the acute respiratory infection?
- If you think it is an ADR, which medicine or medicines might be responsible? How did you arrive at this conclusion?
- What kind of action by the DTC is warranted in this case?

**Activity 3. Serious ADRs with Phen-Fen Combination Medicine**

The combination medicine phenteramine and fenfluramine (commonly called phen-fen) was a popular diet medicine throughout Europe and North America. Like all anti-obesity medicines, this combination leads to tolerance after several months of use, and weight gain invariably occurs when the medicine is discontinued. Short-term effectiveness was dramatic, however, with countless success stories and many patients demanding prescriptions. Safety of this combination was confirmed through the usual premarketing clinical trials. Because phen-fen was another
weight control product, testing and evaluation were extensive, and the approval process was not fast-tracked. Soon after the marketing of the medicine, spontaneous reports began to appear describing serious cardiovascular problems including valvular heart disease and pulmonary hypertension. Spontaneous reports continued until it became obvious that the combination was highly suspect for causing the adverse effect.

- What are some other possible causes for the cardiac conditions listed in the activity?
- What would have prevented this serious side effect from being detected in premarketing trials?
- Why would spontaneous reports be so effective in detecting this ADR after phen-fen’s distribution to the general market?

Summary

Medicine safety issues are critical to a health care system. The DTC is in a position to have a significant impact on preventing and managing these problems. The DTC should have appropriate people to assess the literature carefully to determine the safety of medicines for the formulary. Appropriate management of ADRs should include—

- Assessing the safety of all new medicines before placing them on the formulary
- Implementing systems to monitor the occurrence of ADRs
- Managing and evaluating suspected ADRs, assigning causality and taking corrective action when necessary
- Reporting ADRs to regulatory authorities and manufacturers
- Preventing the occurrence of ADRs and events by—
  - Monitoring the health care system through ADR reporting
  - Carefully evaluating patients before prescribing medications, especially high-risk patients or patients on high-risk medicines
  - Educating staff, especially providers, concerning possible reactions
### Annex 1. Adverse Drug Reaction Reporting Form
(for hospital and primary care clinic use only)

<table>
<thead>
<tr>
<th>Patient and Reaction Information</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>Chart number</td>
<td></td>
</tr>
<tr>
<td>DOB</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td></td>
</tr>
<tr>
<td>Diagnosis for use (indications)</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>Date medicine started</td>
<td></td>
</tr>
<tr>
<td>Date of reaction</td>
<td></td>
</tr>
<tr>
<td>Relevant medical history</td>
<td></td>
</tr>
<tr>
<td>including concurrent pharmaceutical therapy</td>
<td></td>
</tr>
<tr>
<td>Description of ADR</td>
<td></td>
</tr>
<tr>
<td>Outcomes attributed to ADR</td>
<td>1. 2. 3. 4.</td>
</tr>
<tr>
<td>Probability of reaction</td>
<td></td>
</tr>
<tr>
<td>Severity code (see definitions below)</td>
<td>Severe Moderate Minor Incidental</td>
</tr>
<tr>
<td>DTC action—</td>
<td>Yes  No  Yes  No  Yes  No  Yes  No</td>
</tr>
<tr>
<td>• Mark patient’s chart</td>
<td></td>
</tr>
<tr>
<td>• Discuss with prescriber</td>
<td></td>
</tr>
<tr>
<td>• Add to database</td>
<td></td>
</tr>
<tr>
<td>• Report to NDA</td>
<td></td>
</tr>
<tr>
<td>• Report to manufacturer</td>
<td></td>
</tr>
<tr>
<td>Report initiated by:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
</tbody>
</table>
### Severity Assessment Guide

<table>
<thead>
<tr>
<th>Severity of ADR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Fatal or life threatening</td>
</tr>
<tr>
<td>Moderate</td>
<td>Requires antidote, medical procedure, or hospitalization</td>
</tr>
<tr>
<td>Mild</td>
<td>Symptoms are evident and require only the discontinuation of pharmaceutical therapy</td>
</tr>
<tr>
<td>Incidental</td>
<td>Mild symptoms; patient is given option to continue or discontinue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the adverse event appear after the suspected medicine was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Did the adverse reaction improve when the medicine was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the adverse reaction reappear when the medicine was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Are there alternate causes (other than the medicine) that could solely have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>Was the medicine detected in the blood (or other fluids) in a concentration known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the patient have a similar reaction to the same or similar medicines in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the adverse event confirmed by objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total the score to determine the category of the reaction. The categories are defined as follows—

- **Definite**: > 9
- **Probable**: 5–8
- **Possible**: 1–4
- **Doubtful**: 0
SESSION 5. PHARMACEUTICAL QUALITY ASSURANCE

Acknowledgment

Material in session 5 is adapted from Management Sciences for Health’s Managing Drug Supply, chapter 18, “Quality Assurance for Drug Procurement” (MSH 1997).

Purpose and Content

The purpose of quality assurance (QA) in public pharmaceutical supply systems is to make certain that each medicine reaching a patient is safe, effective, and of standard quality. QA activities in a hospital or clinic should be comprehensive, spanning the entire supply process from medicine selection to patient use.

Session 5 was designed to expand your understanding of the determinants of medicine quality. It emphasizes both the technical and managerial actions that can be employed to ensure medicine quality and discusses the role of the Drug and Therapeutics Committee (DTC) in ensuring quality of medicines in the health care system.

Objectives

After completion of this session, participants will be able to—

- Define medicine quality
- Understand how medicine quality is assessed
- Understand how medicine quality is ensured
- Describe the role of the DTC in pharmaceutical quality assurance

Outline

- Key Definitions
- Introduction
- Determinants of Medicine Quality
- How is Quality Assessed?
- How is Quality Assured?
- Important Pharmaceutical Quality Issues for the DTC
- Implications for the DTC

Preparation and Materials

Read—

- Participants’ Guide
- Managing Drug Supply, Chapter 18, “Quality Assurance for Drug Procurement”
• Managing Drug Supply, Chapter 24, “Drug Management for Health Facilities”
• Managing Drug Supply, Chapter 26, “Transport Management”

Further Readings


Key Definitions

Pharmaceutical quality assurance—Pharmaceutical quality assurance may be defined as the sum of all activities and responsibilities required to ensure that the medicine that reaches the patient is safe, effective, and acceptable to the patient.

Pharmaceutical quality control—As defined by WHO, quality control is the part of the firm’s process concerned with medicine sampling, specifications, testing, and the organization’s release procedures that ensure that the necessary tests are carried out and that the materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

Good Manufacturing Practices (GMP)—GMPs are performance standards that WHO and many national governments established for pharmaceutical manufacturers. GMPs are part of the quality assurance activities that ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use and required by drug regulatory authorities. The standards include criteria for personnel, facilities, packaging, quality control, and, in most cases, stability testing.
Session 5. Pharmaceutical Quality Assurance

Introduction

The DTC is responsible for evaluation of new medicines before they are added to the formulary. As discussed in other sessions, this evaluation must involve efficacy, safety, quality, and cost. Session 5 will provide information on how to evaluate and manage the quality of medicines being considered for the formulary.

The purpose of a QA program for hospitals and clinics is to ensure that every medicine reaching a patient is safe, effective, and meets quality standards. A comprehensive quality assurance program includes both technical and managerial activities from selection to patient use. Many areas within a health care system may be involved with quality assurance, including procurement, pharmacy, medical, and nursing departments, as well as the DTC.

Ensuring quality of a product is twofold—

- **Obtaining** quality products that are safe and effective through structured selection and procurement methods
- **Maintaining** quality products through the appropriate storage, distribution, monitoring, and prescribing methods

A comprehensive program will have the following important characteristics—

- Medicines are selected on the basis of safety and efficacy, in an appropriate dosage form with the longest possible shelf life.
- Suppliers with acceptable quality standards are selected.
- Medicines received from suppliers and donors are monitored to meet quality standards.
- Medicine packaging meets contract quality specifications (e.g., blister packs, kits, bulk container specifications).
- Repackaging activities and dispensing practices maintain quality (e.g., appropriate containers and expiration dates).
- Adequate storage conditions in all pharmaceutical areas are maintained.
- Transportation conditions are adequate (e.g., shipping conditions, temperature exposure).
- Product quality concerns reported by inventory managers, prescribers, dispensers, or patients are addressed and resolved.

Poor-quality medicines may cause a number of serious problems including—

- Lack of therapeutic effect that may lead to prolonged illness or death
Determinants or Aspects of Medicine Quality

The following characteristics of a medicine determine its quality—

- **Identity**—The correct active ingredient is present.
- **Purity**—The medicine is not contaminated with potentially harmful substances.
- **Potency**—The correct amount of active ingredient is present, usually between 95 and 110 percent of the labeled amount.
- **Uniformity**—Consistency of, shape, and size of the dosage form do not vary.
- **Bioavailability**—Bioavailability refers to the speed and completeness with which an administered medicine enters the bloodstream. It must be consistent to provide a predictable therapeutic result. Medicine bioavailability differences exist between manufacturers of the same product. Therefore, careful evaluation of generic medicines may be necessary before purchase and use. (See table 1.)
- **Stability**—The activity of the medicine is ensured for the period of time stated on the product label, that is, until the expiration date. (See table 2.)
- **Pharmacopoeial standard**—A medicine is of good quality if its characteristics meet the standards described in a widely accepted pharmacopoeia such as the British Pharmacopoeia (BP), European Pharmacopoeia, International Pharmacopoeia (IP), or United States Pharmacopeia (USP).

**Table 1. Medicines with Known Bioavailability Problems**

<table>
<thead>
<tr>
<th>Medicine 1</th>
<th>Medicine 2</th>
<th>Medicine 3</th>
<th>Medicine 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline</td>
<td>Ergotamine</td>
<td>Levodopa</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Erythromycin</td>
<td>Levothyroxine</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Estrogens</td>
<td>Methyldopa</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Furosemide</td>
<td>Nitrofurantoin</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Glibenclamide</td>
<td>Phenytoin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Iron sulfate</td>
<td>Prednisolone</td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Isosorbide dinitrate</td>
<td>Prednisone</td>
<td></td>
</tr>
</tbody>
</table>

*Source: Adapted from figure 18.1 (MSH 1997).*
Table 2. Medicines Found to Have Stability Problems under Tropical Conditions

<table>
<thead>
<tr>
<th>Oral Solids (tablets)</th>
<th>Oral Liquids</th>
<th>Injectables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>Paracetamol</td>
<td>Ergometrine</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Penicillin V suspension</td>
<td>Methylergometrine</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin V tablets</td>
<td>Retinol</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The lists of medicines in tables 1 and 2 with bioavailability and stability problems represent only a portion of the medicines that may have bioavailability concerns. The U.S. Food and Drug Administration’s “Red Book” (www.fda.gov) lists thousands of products and provides information on bioavailability problems that may exist with some of these medicines. Some examples of bioavailability problems in developing countries include (from Suryawati and Santoso, 1989–95) the following—

- **Rifampicin 450 mg capsules.** When seven brands of this medicine were studied, researchers found a 100 percent variation in peak concentration between the products suggesting that this medicine has a significant bioavailability problems.

- **Captopril.** When six brands of this medicine were studied, peak plasma concentrations varied from 75 ng/ml to 275 ng/ml.

- **Nifedipine.** Peak concentrations varied from 160 ng/ml for a generic medicine to 100 ng/ml for the brand name product.

- **Diclofenac slow release tablets.** Variable release of the active ingredient and subtherapeutic levels were shown with locally manufactured brands when compared to an imported product.

**Critical Elements of a Comprehensive Quality Assurance Program**

**How Is Quality Assessed?**

**Inspection of Shipments**

All shipments of medicines should be quarantined and inspected thoroughly before being released into the supply system. Inspection should include visual inspection and a review of product specifications (including expiration dates) to ensure that the medicine meets specifications.

**Laboratory Testing**

Medicines should be tested in a laboratory to ensure they meet pharmacopoeial standards. Laboratory testing may not be necessary if reputable suppliers with high quality standards are used when medicines are procured. Pharmacopeial standards can be found in international...
pharmacopoeias such as the British Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia, and the United States Pharmacopeia. Medicines that should be tested include—

- Therapeutically critical medicines (cardiovascular and emergency medicines)
- Medicines with known bioavailability or stability problems
- Medicines from new suppliers
- Medicines from suppliers that had quality problems in the past
- Random selection of other medicines to ensure quality

**How Is Quality Assured?**

**Product Selection**

Product selection should be guided by an effective DTC that has thoroughly evaluated the evidence-based information. Preferably, only the dosage forms that have a long shelf-life and are of acceptable stability and bioavailability should be selected.

**Selection of Appropriate Suppliers**

Suppliers need to be carefully selected and qualified so that only reputable companies will be used to supply pharmaceuticals and medical supplies. To ensure the best suppliers, the following need to be done—

- Have the procurement department establish prequalification and registration of suppliers
- For new suppliers, request samples of intended products before delivery for visual inspection and laboratory analysis
- Request specific reports or data for certain medicines (e.g., bioavailability studies)
- Informally gather information from individuals and companies that have experience with the suppliers

**Product Certification**

Obtain appropriate certification of all medicines before accepting for use, including—

- GMP certificate from the drug regulatory authority or from UNICEF Supply Division Warehouse Procurement and Assembly Center (UNIPAC) or other international agency
- Certificate of pharmaceutical product—WHO-type certificate from the drug control agency of exporting country
- Batch certification—certificate of batch analysis or assay from manufacturer, drug regulatory agency, or other international quality control organization
• Random local testing—to confirm quality of the product received

**Contract Specifications**

Contract specifications for all medicines should include at a minimum—

• Pharmacopoeia reference standard
• Local language for product label if necessary
• Standards for packaging to meet specific storage and transport conditions

**Appropriate Storage, Transport, Dispensing, and Use Procedures**

Policies and procedures need to be in place to ensure the appropriate storage, dispensing, and use of all medicines. These procedures should include at a minimum an explanation of the following—

• Pharmaceutical distribution and control procedures (inventory control and management)
• Provision for appropriate storage and transport
• Cold chain procedures that are enforced explicitly
• Appropriate dispensing and use procedures
  o Containers
  o Labeling
  o Counseling the patient
• Avoidance of repackaging unless appropriate quality control is in place

**Product Monitoring System**

The health care system needs a program to monitor the quality of medicines and medical supplies.

*Product Problem Reporting System.* All quality defects must be reported and the pharmacy or procurement department should keep files of these reports. Procurement, pharmacy, and the DTC should periodically evaluate these reports.

The product problem reporting system should be established at the national or local level that specifies the following—

• Who should report the perceived product quality problem
• How the reporting form is to be filled out
• Where and to whom the reporting form should be sent
• What additional measures need to be taken, such as sending samples or information concerning the quantities involved

• What follow-up information will be provided to the person or facility that reported the problem

• What criteria define when a product will receive further testing or be recalled

• How reports of product problems are filed and retrieved for future procurement needs

*Product Recalls.* Product recalls will result from two sources: (a) internally, when a product reporting system identifies unacceptable quality of a product, and (b) from the manufacturer or drug regulatory agency indicating a product has been identified that no longer meets standards for efficacy, safety, or quality. The health care system needs a program to identify, retrieve, and return to the supplier any items that have been recalled or that do not meet quality specifications in the health care system.

A national and local program to handle product recalls, should include the following—

• Rapid communication to facilities for quick product recall
• Inventory control systems that track distribution to facilities by batch number
• Recalls classified according to risk to the consumer, such as—
  - No adverse clinical effect
  - Temporary or mild illness
  - Serious illness
  - Death

• Progress of a product recall to ensure complete compliance

*Who Ensures Medicine Quality?*

Quality of products received in the health care system is the responsibility of many individuals and departments. The procurement department should take the lead role in this endeavor, and the DTC must be an active advisor. The DTC should ensure that all of the departments and individuals listed below are working cohesively to ensure quality products are received.

• Drug Regulatory Authority
  - Registering medicines
  - Inspecting manufacturers for GMP
  - Inspecting pharmacies for compliance with national pharmaceutical policies
  - Sampling and testing medicines as needed

• DTC
  - Selecting medicines for the formulary and procurement
  - Setting technical specifications for pharmaceutical procurement
  - Advising on appropriate storage and transportation of medicines
Coordinating medicine quality testing
Reviewing the quality defect reporting system

- Hospital or Clinic Procurement Office
  - Developing specifications for quality
  - Prequalifying suppliers
  - Inspecting products
  - Reporting, tabulating, and taking action on quality defects

- Pharmacy
  - Controlling quality during repackaging
  - Ensuring appropriate storage in the warehouse, pharmacy, and clinics
  - Using appropriate containers for dispensing
  - Instructing patients in appropriate use of medicines
  - Reporting quality defects

- Physicians
  - Monitoring and promoting quality assurance in their facilities
  - Reporting quality defects

- Patients
  - Storing medicines correctly
  - Taking medicines correctly
  - Reporting quality defects

Pharmaceutical Quality Assurance—Implications for the DTC

The DTC is an important component of the hospital or primary care clinic QA program. The DTC should have an active advisory role on all components of the QA program to ensure that medicine are of the highest quality.

The following discussion focuses on areas in which the DTC should be the most involved and may have the most impact. These areas deal with defining product specifications, providing technical advice to the health care organization, and analyzing quality complaints.

Providing Technical Advice on Procurement of Pharmaceuticals

The DTC is responsible for evaluating and selecting medicines for the formulary and the hospital procurement list. Product specifications for procurement should be developed by the DTC and should include medicine name, strength, form, pharmacopoeial standard, bioavailability standard, and expiration dating. This information is best formulated by the DTC (in conjunction with procurement) because this committee has the expertise and experience to provide the technical information that is required.
The DTC is also responsible for providing technical advice on supplier selection, storage of pharmaceuticals and biologicals, transportation methods to ensure quality, and laboratory testing of high-risk products.

Other important considerations procurement issues include the following—

- **Procurement of generic medicines**

  An important function of the DTC is to obtain quality medicines at reasonable prices. The use of multiple-source generic products that are therapeutically equivalent to another product, but less expensive, is an important concept that will help control cost and maintain a high level of quality in medicine selection. The purchase of generic medicines must provide substitutes that are equivalent in efficacy, safety, and quality.

  A *therapeutically equivalent* product can be defined as a medicine containing the same active ingredient in the same dosage form and of identical strength whose effects with respect to both safety and efficacy are essentially the same. Therapeutic equivalence implies that the product has equivalent bioavailability or is bioequivalent. Generic medicines that have the same active ingredients may not have the same bioavailability.

- **Specifying bioavailability**

  Bioavailability refers to the speed and the extent of absorption of a medicine’s active ingredient in the bloodstream. Bioavailability of generic products may differ between manufacturers of the same product. Procurement departments must obtain bioavailability data when ordering medicines and must not change manufacturers of a generic product unless bioequivalence of the new product can be assured. Bioavailability data, including laboratory test results, can be obtained from many manufacturers. Any requirements for this data should be included in the tender documents and final contracts with the suppliers. (See table 1 for a list of medicines with known bioavailability problems.)

- **Stability of medicines**

  Stability of a product is of considerable concern and refers to its capacity to maintain potency throughout its shelf life (i.e., until the expiration date). Stability can be ensured, to some degree, by asking for stability studies on products that have known problems and by ensuring that all products are received, stored, and transported at appropriate conditions, avoiding direct light, temperature extremes, and moisture. Reputable manufacturers will continue to test products throughout the stated shelf life to confirm that the medicine retains its full potency.

  Medicines with known stability problems must be handled carefully by the hospital or clinic. These medicines may deteriorate more rapidly than expected, especially in tropical conditions of elevated heat and humidity. Stability testing in the country of purchase may be necessary to ensure that these products indeed have stability throughout the shelf life of the product. (See table 2 for a list of medicines with known stability problems.)
Providing Technical Advice to Other Departments

The DTC should work closely with hospital and clinic departments, including pharmacy, nursing, medical, and supply management staff, to ensure that pharmaceutical quality assurance procedures are practiced throughout the system. All health care personnel should be enlisted and encouraged to participate in a comprehensive QA program to ensure that medicines are procured, stored, administered, dispensed, and used correctly.

Analyzing Product Problem Reports

The DTC should work with drug regulatory agencies, the procurement department, suppliers, pharmacies, physicians, and patients to analyze, evaluate, and take action on quality complaints of products. This function of the DTC is vital to ensure that medicines of good quality are available. Complaints about quality should be analyzed and recommendations developed to deal with quality defects. A medicine recall system must be readily available and effective.

Even the best QA program of a manufacturer, supplier, and a hospital or health clinic may allow a defective product to slip through the system. In addition, many health care professionals and patients will have erroneous perceptions of product quality (e.g., appropriate manufacturers or relationship of price and quality), which makes the requirement for a monitoring system essential.

Activity 1. Quality Assurance Issues and Concerns

List the specific quality assurance concerns in your programs in hospitals and primary care clinics under the following headings—

- Obtaining quality products (source issues): problems with the quality of medicines being supplied by commercial sources, government production, or donors
- Maintaining quality products (supply system issues): problems with quality assurance at the central warehouse, in transit, at local facilities, and the like
- Examples of poor quality: anecdotes illustrating poor quality that do not clearly fit under the above headings

As a part of this exercise, please answer the following questions concerning your quality assurance programs—

1. Are you satisfied with the quality of medicines you receive?
2. Is quality maintained throughout your distribution network?
3. Are there complaints of poor quality by patients or health workers?
4. Is there a formal mechanism for reporting and investigating product quality complaints?

5. What role do you see for the DTC in improving and maintaining quality in your health care system?

6. Does anyone have a particular quality assurance issue with which he or she needs help?

**Summary**

Quality assurance is the responsibility of many different programs and individuals, including procurement, pharmacy, medical staff, patients, and the DTC. A coordinated effort is required to ensure that all departments work together in dealing with quality assurance. Pharmaceutical quality assurance must have a high priority within the health care system in order for the hospital or clinic to have medicines that are effective, safe, acceptable in quality, and at reasonable cost. The consequences of poor quality products may lead to ineffective, inappropriate treatment as well as increased cost for the health care system.

A comprehensive quality assurance program should be involved with obtaining quality products and maintaining this quality. Table 3 lists the activities that are needed, at a minimum, to assure that quality products are available to the patient.

**Table 3. Minimum Activities Needed to Assure Quality**

<table>
<thead>
<tr>
<th>Assuring Quality</th>
<th>Assessing Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select medicines, dosage forms, and packaging to ensure quality</td>
<td>Inspection of medicines</td>
</tr>
<tr>
<td>Use prequalified suppliers</td>
<td>• Visual</td>
</tr>
<tr>
<td>Use product certification</td>
<td>• Specifications review</td>
</tr>
<tr>
<td>Prepare and enforce quality-related contract specifications</td>
<td>Laboratory testing when necessary</td>
</tr>
<tr>
<td>Ensure appropriate storage, transport, dispensing, and use</td>
<td></td>
</tr>
<tr>
<td>Establish and use product monitoring systems</td>
<td></td>
</tr>
</tbody>
</table>


Drug and Therapeutics Committee
Training Course

Session 6.
Evaluating the Cost of Pharmaceuticals
SESSION 6. EVALUATING THE COST OF PHARMACEUTICALS

Purpose and Content

Session 6 is designed to provide participants with basic information about analyzing the cost of pharmaceuticals and, to a limited extent, pharmacoeconomic principles. Participants will learn the value of a basic cost analysis and its importance to the Drug and Therapeutics Committee (DTC) in evaluating and selecting medicines for the formulary.

Objectives

After attending this session, participants will be able to—

- Define and understand the different types of cost analysis methods relevant to choosing medicines for the formulary
- Understand how to read and assess journal articles concerning an economic study
- Apply session materials to conduct a basic cost analysis for a medicine being requested for the formulary

Preparation and Materials

Read the Participants’ Guide.

Further Readings


Key Definitions

Pharmacoeconomics—The description and analysis of the cost of pharmaceutical therapy to health care systems and society

Cost—The total resources consumed in producing a good or service

Price—The amount of money required to purchase an item
Medicine effectiveness—The effects of a medicine when used in real-life situations

Medicine efficacy—The effects of a medicine under clinical trial conditions

Introduction

The Drug and Therapeutics Committee (DTC) is responsible for careful evaluation of new medicines before they are added to the formulary. As discussed in previous sessions, this evaluation must involve efficacy, safety, quality, and cost. Session 6 provides information on how to evaluate the cost of a medicine, not only its procurement cost, but also the cost impact on the entire health care system including the patient. The discussion is important so that the overall evaluation of a medicine is complete and the DTC knows all of the cost implications when considering the addition of a new medicine. Economic evaluation techniques are used not only for medicines, but also for health care services such as disease management programs. Two questions can be answered by economic evaluation—

- Is this health procedure, service, or program worth doing compared with other things the DTC could do with these same resources?
- Is the DTC satisfied that the health care resources should be spent in this way rather than some other way?

The medicine information literature has an excess of articles, from research to clinical practice, describing the various uses of cost analysis in pharmaceutical management programs. The science of pharmacoeconomics is relatively new, however, and many of the concepts are not well understood by practitioners. When applied appropriately, pharmacoeconomic principles are useful to determine which medication or other intervention will provide the most benefit. Many pharmacoeconomic studies, however, are sponsored by a pharmaceutical company to prove economic superiority of its produce over a competing medication, especially when comparing medicines of similar efficacy and safety. The nature of the pharmacoeconomic discipline allows for the development of a study to meet a particular outcome and, therefore, the reader of economic studies must evaluate them carefully.

The quality of pharmacoeconomic studies is frequently poor, and the reader of any study must take quality into consideration. This session concentrates on the basic aspects of pharmacoeconomics so that participants will be able to use key concepts and ideas to evaluate medicines for the formulary. Participants are referred to the key readings to provide more detailed information on the pharmacoeconomic discipline.

Cost of a Medicine

What actually goes into the cost of a medicine? The most basic cost of a pharmaceutical is reflected in the acquisition price from a supplier. Acquisition cost is one of the most important aspects in calculating a medicine’s cost, but it is only a start in the total evaluation. It is
becoming more important to look beyond the acquisition cost of a medicine and obtain all costs associated with using the medicine.

There are three types of costs associated with medicines in a health care system: direct, indirect, and intangible. These three types of costs, when taken collectively, will give the most comprehensive assessment of actual medicine cost.

- **Direct costs** are costs that are directly related to the resource use associated with a service or commodity in dealing with a health care intervention and include—
  - Acquisition cost of the medicine (medicine price)
  - Transportation (shipping and insurance)
  - Supplies and equipment to administer the medicine
  - Supply management (storage facilities, supply personnel)
  - Medical and allied health consultations
  - Costs of managing adverse effects of therapy
  - Hospitalization costs related to adverse events or treatment effectiveness
  - Laboratory services
  - Outpatient visits
  - Nonmedical costs such as travel costs, community assistance, and palliative care

- **Indirect costs** are costs associated with lost production capacity and include—
  - Time lost from work for the patient
  - Time lost from work for the caregiver

- **Intangible costs** are costs associated with pain and suffering, usually incorporated in the utilities assigned to health states that reflect quality of life.

**Economic Evaluation Methods**

Economic evaluation is about relating the cost of a service or program to the outcomes delivered. Usually, analysts are interested in comparing one health product or intervention with another. There are generally four technical types of economic evaluations—

- **Cost minimization analysis** (CMA) assumes that the effects of the two interventions being compared are equal and therefore compares costs.

- **Cost effectiveness analysis** (CEA) is used when the effects of the two interventions being compared are different (i.e., one intervention is superior to the other).

- **Cost-utility analysis** (CUA) is a special type of cost effectiveness analysis, in which the outcome is expressed as a utility measure (e.g., quality-adjusted life year [QALY]).

- **Cost-benefit analysis** (CBA) is derived from transport economics; both costs and benefits are expressed in monetary terms.
For assessing pharmaceuticals, the first three types of evaluation are commonly used. Cost-benefit analysis is far more challenging to carry out and interpret for health interventions, so papers describing cost-benefit analyses of pharmaceuticals should be interpreted with care.

**Cost-Minimization Analysis**

CMA is appropriate when two interventions have been shown to produce the same, or similar, effects. In such a situation, only the costs of the interventions need to be considered. For comparing two pharmaceutical products, cost minimization can be used only for products that have been shown to be equivalent in therapeutic effect. Therefore, this method is most useful for comparing generics and their therapeutic equivalents or “me too” medicines. This type of comparison can be difficult for many products because there may not be a reliable equivalence between the two products. If therapeutic equivalence cannot be demonstrated, then this particular type of cost comparison should not be used.

The costs to be included in the analysis include the intervention, or medicine costs, along with other health service costs including medical staff costs (e.g., physicians, nurses), laboratory costs, and equipment costs (e.g., syringes, IV sets). The inclusion of indirect costs related to such things as time off work and lost productivity is not straightforward because the valuation of indirect costs is problematic. If such costs are included, then care should be taken in the valuation process.

To perform a CMA, the following costs should be identified, measured, and then valued—

- Acquisition cost of the medicine
- Pharmacy, nursing, and physician costs (if they contribute significantly to the cost of using the medicine)
- Cost of equipment and supplies (e.g., syringes, needles, IV sets, sterile water for dilution)
- Cost of laboratory services (if a significant cost is involved)
- Indirect costs (such as time off work), but only if they can be measured and valued reliably

Table 1 is an example of a CMA of two injectable antibiotics for treating meningitis.
Table 1. Sample CMA (Based on Course of Treatment)

<table>
<thead>
<tr>
<th>Cost Centers</th>
<th>Medicine A (USD)</th>
<th>Medicine B (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition price</td>
<td>8.00</td>
<td>15.00</td>
</tr>
<tr>
<td>Pharmacist salary (to prepare the medicine)</td>
<td>2.50</td>
<td>1.50</td>
</tr>
<tr>
<td>Nursing salary (to administer the medicine)</td>
<td>2.50</td>
<td>2.00</td>
</tr>
<tr>
<td>Supplies (to administer the medicine)</td>
<td>9.00</td>
<td>2.25</td>
</tr>
<tr>
<td>Laboratory services</td>
<td>4.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26.00</strong></td>
<td><strong>21.75</strong></td>
</tr>
</tbody>
</table>

*Note: USD = U.S. dollars.*

The CMA in table 1 shows that medicine B is slightly less costly to use than medicine A. Just looking at acquisition price of the medicines, however, would have shown that medicine A was less costly and probably preferred if all other criteria for selection were equal. Completing the CMA provides information indicating that the real cost of the two medicines is significantly different from the acquisition price and that medicine B has a lower overall cost.

Table 2 shows another example of a CMA. In this example, the total annual cost is included, a fact that is also important for the DTC to consider.

Table 2. Hypothetical Example of Cost Minimization Analysis of Three Injectable Antibiotics

<table>
<thead>
<tr>
<th>Cost Categories</th>
<th>Ampicillin (500 mg)</th>
<th>Ceftriaxone (1 g)</th>
<th>Gentamicin (80 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition price for one vial</td>
<td>USD 1.00</td>
<td>USD 8.00</td>
<td>USD 2.00</td>
</tr>
<tr>
<td>Doses per day</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Price per day</td>
<td>USD 4.00</td>
<td>USD 8.00</td>
<td>USD 6.00</td>
</tr>
<tr>
<td>Nursing salary at USD 0.75 per injection</td>
<td>USD 3.00</td>
<td>USD 0.75</td>
<td>USD 2.25</td>
</tr>
<tr>
<td>Equipment: IV set at USD 1.00 per set</td>
<td>—</td>
<td>USD 1.00</td>
<td>—</td>
</tr>
<tr>
<td>Syringe + needle USD 0.50 per set</td>
<td>USD 2.00</td>
<td>—</td>
<td>USD 1.50</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>USD 2.00</td>
<td>USD 2.00</td>
<td>USD 4.00</td>
</tr>
<tr>
<td><strong>Total medicine costs /day</strong></td>
<td>USD 11.00</td>
<td>USD 11.75</td>
<td>USD 13.75</td>
</tr>
<tr>
<td>3,000 treatment-days/year</td>
<td>3,000 days</td>
<td>3,000 days</td>
<td>3,000 days</td>
</tr>
<tr>
<td><strong>Total medicine costs</strong></td>
<td>USD 33,000</td>
<td>USD 35,250</td>
<td>USD 41,250</td>
</tr>
</tbody>
</table>

Sensitivity analyses are 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 2, if we change the assumption that giving an IV injection by IV infusion takes the least nursing time, and assume instead that such infusions take slightly more nursing time than ampicillin or gentamicin, such that the nursing salary would be USD 4 instead of USD 0.75, then the overall cost of using ceftriaxone would be USD 15 per day and total annual cost USD 45,000. In this scenario, ceftriaxone would be the most costly option.
Cost-Effectiveness Analysis

CEA is a type of economic evaluation that compares the costs and outcomes of health programs or treatments when the interventions have a common health outcome but differ in effectiveness. The health outcomes are measured in natural units (e.g., lives saved, life years gained, cases of illness avoided) or changes in functional status (e.g., units of blood pressure in hypertension, cholesterol in hypercholesterolemia). The results of a CEA are generally displayed as a cost per unit of effect. With regard to medicines, CEA is used to compare two or more medicines that are not exactly equivalent in terms of dose or therapeutic effect, but that are used to treat the same clinical condition. This form of analysis is difficult and is often done only at the national level. It requires measuring the cost per defined measurable clinical outcome (effect) for each of the medicines. The cost of the medicine should include indirect as well as direct costs, and some examples of measures for clinical outcomes include—

- Hypertension—blood pressure measurements
- Diabetes—glycosylated hemoglobin (HbA1c), 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, QALYs, or disability-adjusted life years (DALYs)

Cost-effectiveness measurement can be presented in many different ways, for example, for—

- Acute illness: cost per course of treatment or cost per cure
- Chronic illness: cost per month of satisfactory control
- Disease prevention: cost per case prevented
- Health promotion: cost per month of desired outcome

Steps to Complete a Basic CEA

1. Define the objective of the analysis. For example, which pharmaceutical regimen should be the treatment of choice?

2. Identify the different ways to achieve the objective. For example, should a cheaper, slightly less efficacious medicine or a more expensive, slightly more efficacious medicine be chosen?

3. Identify and measure the intervention and pharmaceutical 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 (CER), or the cost per unit of benefit of the health care intervention (e.g., medicine), is estimated by dividing the total intervention or medicine cost by the number of units of outcome. The incremental cost-effectiveness ratio (ICER) is the change in costs and health benefits when one health care intervention (e.g., medicine A) is compared with the alternative intervention (e.g., medicine B). The formula below demonstrates how the ICER is calculated.

\[
\text{ICER} = \frac{\text{Cost of intervention A} - \text{Cost of intervention B}}{\text{Effect of intervention A} - \text{Effect of intervention B}}
\]

If intervention A is superior to intervention B and costs less, then intervention A is said to be dominant. If intervention A has greater benefit but also costs more than intervention B, then the ICER is used in determining whether the benefits gained from intervention A are worth the additional cost.

6. Perform a sensitivity analysis on the conclusions. A sensitivity analysis varies some of the assumptions in the analysis (e.g., costs of staff salaries and hospital overheads) 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.

**Example: Using CEA for Pharmaceutical Treatment of Type II Diabetes**

Table 3 provides a summary of the cost information needed to perform a simple cost-effectiveness analysis of two drugs, A and B, used in the treatment of Type II diabetes, assuming a treatment duration of one year. The desirable outcome from treatment is more patients with a lower HbA1c, a measure of control of diabetes. Table 4 provides the incremental cost, benefit (percentage of patients with ≥ 1% decrease in HbA1c), and resultant ICER.

**Table 3. Cost Information for CEA**

<table>
<thead>
<tr>
<th>Cost</th>
<th>Cost/Unit (USD)</th>
<th>No. of Units</th>
<th>No. of Patients</th>
<th>Total Cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine cost</td>
<td>40</td>
<td>12</td>
<td>100</td>
<td>48,000</td>
</tr>
<tr>
<td>Laboratory cost</td>
<td>20</td>
<td>1</td>
<td>100</td>
<td>2,000</td>
</tr>
<tr>
<td>Adverse event</td>
<td>50</td>
<td>2</td>
<td>100</td>
<td>10,000</td>
</tr>
<tr>
<td>Physician</td>
<td>25</td>
<td>2</td>
<td>100</td>
<td>5,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>65,000</td>
</tr>
<tr>
<td>Medicine B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine cost</td>
<td>25</td>
<td>12</td>
<td>100</td>
<td>30,000</td>
</tr>
<tr>
<td>Laboratory cost</td>
<td>20</td>
<td>2</td>
<td>100</td>
<td>4,000</td>
</tr>
<tr>
<td>Adverse event</td>
<td>50</td>
<td>3</td>
<td>100</td>
<td>15,000</td>
</tr>
<tr>
<td>Physician</td>
<td>25</td>
<td>3</td>
<td>100</td>
<td>7,500</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>56,500</td>
</tr>
</tbody>
</table>
Table 4. Results of CEA

<table>
<thead>
<tr>
<th>Component</th>
<th>Medicine A</th>
<th>Medicine B</th>
<th>Increment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>USD 65,000.00</td>
<td>USD 56,500.00</td>
<td>USD 8,500.00</td>
</tr>
<tr>
<td>Number of patients per 100 treated with ≥1% decrease in HbA1c</td>
<td>25</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Cost-effectiveness ratio</td>
<td>65,000/25 = 2,600</td>
<td>56,500/19 = 2,973.70</td>
<td>USD 1,416.67</td>
</tr>
<tr>
<td>Cost per extra patient with ≥1% decrease in HbA1c with medicine A compared to medicine B: (65,000 – 56,500) / (25 – 19) = 8,500 / 6 = 1,416.67</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 demonstrates that medicine A is more effective than medicine B because more patients get a desirable response (i.e., 25 patients per 100 with medicine A as compared to 19 patients per 100 with medicine B). The CER is lower with medicine A—USD 2,600.00 to treat one patient successfully (by reducing HbA1c ≥ 1 percent), than with medicine B—USD 2,973.70 to treat one patient successfully. A CER, however, expresses only the cost-effectiveness of an intervention compared to no intervention and cannot be used directly to make comparisons between different interventions. The DTC, by contrast, wants to compare medicine A directly with medicine B and for this comparison, the ICER must be calculated. In this example, the incremental cost per extra patient with ≥1 percent decrease in HbA1c is calculated as USD 8,500.00/6, which is USD 1,416.67, meaning that the health care system would have to pay an extra USD 1,416.67 (over a year) for each extra patient with a desirable response. The judgment that needs to be made is whether this estimate represents value for money.

Table 5 below provides the components of a CEA and a brief description of each component.

Table 5. Components of a CEA

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Context</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Intervention</td>
<td>Pharmaceutical treatment or health program</td>
<td></td>
</tr>
<tr>
<td>2. Population</td>
<td>Based on clinical history, age, gender, other characteristics</td>
<td>The population should be relevant to or comparable to the population in which the treatment will be used.</td>
</tr>
<tr>
<td>3. Setting</td>
<td>Location, type of institution</td>
<td>Does the trial setting correspond to the setting in which medicine or treatment will be used?</td>
</tr>
<tr>
<td>4. Comparator</td>
<td>Treatment most likely to be replaced; standard medical management</td>
<td>The basis on which comparator is chosen is important (i.e., more expensive comparator may make new treatment more cost-effective).</td>
</tr>
<tr>
<td><strong>Comparative Efficacy</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 5. Source of evidence | • Published literature • Clinical trials | The source of evidence should be evaluated using the following criteria— • Quality of evidence—randomization, trial size,
<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
<th>Issues</th>
</tr>
</thead>
</table>
| **Effect size** | | - Relevance of evidence—similarity of trial settings, populations, and other characteristics to the situation in which treatment will be used  
  - Comprehensiveness of evidence—representative of medical literature as a whole or selective |
| 6. Outcomes used | Surrogate or final outcome | - Surrogate outcomes must be relevant.  
  - Surrogate and final outcomes must be linked. |
| **Costs** | | |
| 7. Identification |  
  - Perspective of the analysis (societal, patient, government)  
  - Type of costs |  
  The following costs should be identified—  
  - Medicine or treatment costs  
  - Physician costs  
  - Administration costs  
  - Laboratory monitoring costs  
  - Adverse event costs  
  - Other medical services  
  - Indirect costs |
| 8. Measurement | Number of units consumed | - Does use in trials represent use in real life?  
  - The accuracy of medical records should be checked. |
| 9. Valuation | Cost per unit | The source of cost should be determined. |
| 10. Discounting | Rate used to convert the value of future costs and consequences into equivalent present values | WHO recommends a discount rate of 3% for costs and benefits and a sensitivity analysis using 6% for costs and 0% for benefits. |
| 11. Sensitivity analyses | Determines the sensitivity of the estimates to variations in cost and treatment effects | The following elements need to be considered—  
  - Confidence interval of the point estimate of treatment effect  
  - Costs  
  - Discount rate  
  - Duration |

Box 1 shows a real-life 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 tissue plasminogen activator.
Comparison was done in terms of (a) total treatment costs, (b) death rates, and (c) cost per life saved (or death averted). The treatment costs included all the direct and indirect costs.

**Box 1. Economic Analysis of Two Thrombolytics in Acute Myocardial Infarction in Australia**

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

**Cost of treatment and mortality rates**
- Usual care (UC) of MI: 3.5 million Australian dollars (AUD)/1,000 cases, 120 die
- UC of MI + streptokinase (SK): AUD 3.7 million/1,000 cases, 90 die
- UC of MI + tissue plasminogen activator (tPA): AUD 5.5 million/1,000 cases, 80 die

**Comparison of the different treatments**
- **Difference between SK and UC of MI:**
  - Cost of treatment = AUD 3.7 – 3.5 million/1,000 cases = AUD 0.2 million/1,000 cases = AUD 200 per case
  - Number of deaths that will be prevented = 120 – 90 = 30 deaths/1,000 cases treated
  - Cost effectiveness of SK = AUD 0.2 million/30 lives = AUD 6,700 per life saved

- **Difference between tPA and usual care of MI:**
  - Cost of treatment = AUD 5.5 – 3.5 million/1,000 cases = AUD 2.0 million/1,000 cases = AUD 2,000/case
  - Number of deaths that will be prevented = 120 – 80 = 40 deaths/1,000 cases treated
  - Cost effectiveness of tPA = AUD 2.0 million/40 lives = AUD 50,000 per life saved

- **Difference between tPA and SK treatments for MI:**
  - Cost of treatment = AUD 2.0 – 0.2 million/1,000 cases = 1.8 million/1,000 cases = AUD 1,800 per case
  - Number of deaths that will be prevented = 90 – 80 = 10 deaths/1,000 cases treated
  - Increased cost effectiveness of tPA over SK = AUD 1.8 million/10 lives = AUD 180,000 per life saved

**If one has a budget of only AUD 500,000, which medicine should one use?**
- For SK: number of cases that can be treated = 500,000/200 = 2,500 cases
  - number of lives that can be saved = (30/1000) × 2500 = 75 lives

- For tPA: number of cases that can be treated = 500,000/2000 = 250 cases
  - number of lives that can be saved = (40/1000) × 250 = 10 lives

**Conclusion**
This study concluded that though tPA had slightly better efficacy 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 effectiveness of tPA over SK was so high (AUD 180,000 per life saved) that fewer people could be treated, and fewer lives saved, using tPA as compared to SK, with the limited budget available.

**Sources:**
Other Types of Economic Evaluation

Cost-Utility Analysis

CUA is a type of economic evaluation that uses utilities as a measure of the value of an intervention. Utilities, which are measured as the preferences individuals or society may have for any particular set of health outcomes, are expressed as numerical values between 0 (worst) and 1 (full health). The outcome used in a cost utility evaluation is a QALY or DALY that includes the length of life gained and a measure of the subjective levels of well-being. QALYs are determined by adjusting the length of time affected through the health outcome by the utility value of the resulting level of health status. In a CUA the incremental cost of an intervention is compared to the incremental health improvement attributable to the intervention, with the health improvement measured in QALYs gained. The results of CUAs are usually expressed in terms of the cost per QALY gained.

A number of methods are used to measure and estimate utilities. The sources of values used in the analysis can come from patients, health care providers, or the general public. Further details of these methods can be found in Drummond et al. (2005) and are beyond the scope of this session.

Using CUA in relation to pharmaceuticals has three weaknesses: (a) utility as a strength of preference may not be a reliable or comprehensive index of health-related quality of life; (b) QALY calculations may not capture precisely the real trade-offs between quantity and quality of life; and (c) the methods used to work out numerical values for utilities are not comparable, may be unreliable, and may not translate well from one setting to another. If a DTC wants to use CUA in decision making, it should make sure that the study can be evaluated by an expert.

Cost-Benefit Analysis

A CBA is an economic evaluation that measures both the costs and benefits of treatment alternatives in monetary amounts. The results of a CBA can be stated as a ratio of benefits to costs or as a simple difference representing the net benefit of one alternative over another. Results of such analyses are expressed as benefit-to-cost ratios. They are difficult to carry out reliably for pharmaceuticals and should not be used in decision making by DTCs without expert advice on their validity and interpretation.

Two Important Components of Economic Evaluations

Sensitivity Analysis

Sensitivity analysis should be done for all kinds of economic evaluation—whether cost minimization, cost-effectiveness, or some other type. This technique is used to quantify the uncertainty in an economic evaluation by varying the values given to a key variable in the valuation. Key variables are identified, a plausible range of values is determined, and then the analysis is re-run using different values of the key variables, and the impact of these changes on the results is observed. Sensitivity analysis can be conducted changing one variable at a time.
(one-way) or several (multi-way). If the results of an economic evaluation change significantly with sensitivity analysis, they are generally less reliable for use in decision making.

Examples of variables in a cost-analysis study include cost of physician visits, price of medicines, cost estimate of adverse drug reactions (ADRs) as well as the number of ADRs experienced, laboratory tests required in the treatment, and duration of treatment. In a sensitivity analysis, different estimates of cost can be applied to the variables and the analysis performed to confirm or refute the original results. (See the example following table 2 in “Cost-Minimization Analysis” above.)

**Discounting**

Discounting is a technique used in economic evaluations that allows the adjustment of calculations of costs and benefits over time for the different preference we have for having costs in the present or in the future. The discount rate is the rate used to convert the value of future costs and benefits into equivalent present values. The choice of discount rate and whether it should be applied to costs, benefits, or both are controversial issues—some authors argue that benefits should not be discounted. Typical discount rates range from 3 to 6 percent. The important point to note is that different discount rates can dramatically alter the final result of any cost-effectiveness calculation, a point to consider when deciding whether a DTC can rely on an analysis.

**Evaluating Pharmacoeconomic Studies**

Unlike clinical studies that involve medicine comparisons for efficacy, there is no “gold standard” for pharmacoeconomic studies. Several different methods of performing these studies are used, and outcomes are highly dependent on how the analysis was performed. Using published pharmacoeconomics studies has a number of potential pitfalls, so readers of this literature must be careful when interpreting results and take the following into account.

- One significant problem is the applicability of a study for one’s home country or community—what may make sense economically in one area of the world may not be applicable in other areas.
- The randomized controlled study is the most reliable medicine study design. Unfortunately the rigorous nature of a clinical trial frequently does not reflect what will happen in other locations that do not have the same constraints as the study (i.e., blinding, monitoring, laboratory testing, intense medical follow-up).
- The rush to conduct pharmacoeconomic studies has resulted in variations in the quality of many studies performed. Problems include using incorrect methodology, arriving at incorrect conclusions, and defining important pharmacoeconomic terms incorrectly.
- Many studies are conducted by pharmaceutical companies. There is always the possibility of bias being introduced concerning the information about the company’s medicine.
• Negative outcome research seldom gets into the literature. This omission again may relate back to the sponsor of the study, who may want to suppress any results that are not useful in promoting a particular medicine.

Readers should interpret published data cautiously. Some fundamental questions that a reader must ask about an economic evaluation are—

• Are the patients and therapies selected for the study similar to those in my community?
• Is the study applicable to my setting?
• Are costs of the therapies fully described and similar to those for my patients?
• Are costs of benefits or assumptions of effectiveness fully disclosed?
• Has a sensitivity analysis been done?
• Who is the sponsor?
• Are all of the costs associated with pharmaceutical treatment including good and bad outcomes described (not just prices)?

• Has discounting been used to reflect the cost of future benefits or consequences in present day values?

A checklist for assessing economic evaluations was adapted from one found in Methods for the Economic Evaluation of Health Care Programmes, 3rd ed. by M. J. Drummond, G.W. Sculpher, B.J. Torrance, et al. 2005, Oxford University Press. Systematic application of the points on the checklist (appendix 1) will allow readers to identify and assess the strengths and weaknesses of individual studies.

**Activity 1. Cost Minimization Analysis of NSAIDs**

Your hospital outpatient department sees a large volume of patients with back pain, minor trauma, and arthralgias. A medicine use indicator study in this department indicated that a high percentage—25 percent—of patients receive injections. An in-depth review showed that diclofenac injection is extensively used for all type of pain syndromes. Typically, patients are given diclofenac 75 mg intramuscular (IM) followed by diclofenac 50 mg three times a day for one week.

Review of the literature on use of this injection shows that it is no more effective than oral non-steroidal anti-inflammatory drugs (NSAIDs) and has significant ADRs including pain on injection and occasional neuropathies. Your DTC asks that a cost minimization study be done to evaluate the four NSAIDs that are available in the outpatient department.

For activity 1, perform a cost analysis (cost-minimization) of these medicines based on the usual treatment regimen of seven days. Acquisition costs of these products are listed in table 6.
Table 6. Acquisition Costs

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
<th>Cost per Dose (Acquisition)</th>
<th>Cost per Day (Treatment)</th>
<th>Cost for 7 Days (Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>400 mg tid</td>
<td>0.0077</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>500 mg bid</td>
<td>0.0216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50 mg tid</td>
<td>0.0057</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac injection</td>
<td>75 mg IM × 1 dose only</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Diclofenac 50 mg tid</td>
<td>50 mg tid</td>
<td>0.0057</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Other cost associated with administering NSAIDs injections include—
- Syringe/needle: USD 0.90
- Nursing cost to administer one dose (salary): USD 1.00

1. What is the least costly treatment regimen according to your analysis?

2. What is the cost savings for 1,000 patients treated with diclofenac tablets compared to regimen of diclofenac injection + diclofenac tablets?

3. Perform a sensitivity analysis on your analysis by changing the cost of syringe/needle to USD 1.50

4. What would your DTC recommend concerning the NSAIDs in this health facility?

Activity 2. Cost-Effectiveness Analysis of Two Antimalarial Treatments

Your DTC is considering adding an artemisinin combination therapy for the treatment of uncomplicated malaria. You have two choices to consider: artesunate plus lumefantrine (A+L) or artesunate plus mefloquine (A+M).

The effectiveness of both medicines has been summarized in a systematic review—
- A+L, 6 doses: number of patients with parasitemia at 28 days was 11 of 289 (4 percent)
- A+M, 3 days: number of patients with parasitemia at 28 days was 0 of 100 (0 percent)

The dose of A+L in adults is six doses of four tablets (20 mg + 120 mg). The dose of A+M in adults is four tablets of artesunate daily for three days (200 mg per day), and 500 mg of mefloquine on day 2 and 250 mg on day 3 (for 50 kg adult).

The cost of one pack of 24 A+L tablets is USD 5.00. The cost of A+M (two separate packets) is USD 1.54 for 12 artesunate 50 mg tablets and USD 4.57 for six mefloquine 250 mg tablets.

1. Evaluate the cost-effectiveness of A+M compared to A+L.
2. Carry out a simple sensitivity analysis, by reducing the effectiveness of A+M to 5 percent lower than that of A+L. What other important criteria should be considered when adding such a medicine to the formulary?

3. Which of these two medications is the preferable product for the formulary?

**Summary**

Economic evaluation is an important component in evaluating the usefulness of a medicine for the formulary. A simple determination of a medicine’s price is frequently inadequate for determining the actual cost of a medicine to the health care system.

Basic economic evaluations can be done by the DTC, most commonly cost-minimization analysis. Cost-effectiveness can also be done but usually only in large centers or at the national level where there is sufficient expertise. Nevertheless, the DTC can also use pharmacoeconomic information from clinical trials or reasonable extrapolations of these trials in assessing medicines for the formulary.

Most likely, health care practitioners will increasingly be faced with the need to conduct or evaluate medicine costs in the future because health care systems will demand that such data be carefully considered before adding a new medicine to the formulary.
Appendix 1. Checklist for Assessing Economic Evaluations

The following 10-point checklist for assessing economic evaluations has been adapted from Drummond et al. (2005). Systematic application of the points on the checklist will allow readers to identify and assess the strengths and weaknesses of individual studies. This checklist is made available by permission of Oxford University Press (www.oup.com).

1 Was a well-defined question posed in answerable form?

1.1 Did the study examine both costs and effects of the service(s) or program(s)?

1.2 Did the study involve a comparison of alternatives?

1.3 Was a viewpoint for the analysis stated, and was the study placed in any particular decision-making context?

2 Was a comprehensive description of the competing alternatives given (i.e., can you tell who did what to whom, where, and how often)?

2.1 Were any relevant alternatives omitted?

2.2 Was (should) a do-nothing alternative (be) considered?

3 Was the effectiveness of the programs or services established?

3.1 Was effectiveness established through a randomized, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?

3.2 Were effectiveness data collected and summarized through a systematic overview of clinical studies? If so, were the search strategy and rules for inclusion or exclusion outlined?

3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4 Were all the important and relevant costs and consequences for each alternative identified?

4.1 Was the range wide enough for the research question at hand?

4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)

4.3 Were capital costs, as well as operating costs, included?
5  Were costs and consequences measured accurately in appropriate physical units (e.g., hours of nursing time, number of physician visits, lost workdays, gained life years)?
   5.1  Were the sources of resource utilization described and justified?
   5.2  Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
   5.3  Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6  Were costs and consequences valued credibly?
   6.1  Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy makers’ views and health professionals’ judgments.)
   6.2  Were market values employed for changes involving resources gained or depleted?
   6.3  Where market values were absent (e.g., volunteer labor) or market values did not reflect actual values (such as clinic space donated at a reduced rate) were adjustments made to approximate market values?
   6.4  Was the valuation of consequences appropriate for the question posed (i.e., has the appropriate type or types of analysis—cost-effectiveness, cost-benefit, cost-utility—been selected)?

7  Were costs and consequences adjusted for differential timing?
   7.1  Were costs and consequences that occur in the future discounted to their present values?
   7.2  Was any justification given for the discount rate used?

8  Was an incremental analysis of costs and consequences of alternatives performed?
   8.1  Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9  Was allowance made for uncertainty in the estimates of costs and consequences?
   9.1  If patient-level data on costs or consequences were available, were appropriate statistical analyses performed?
   9.2  If a sensitivity analysis was employed, was justification provided for the range of values (for key study parameters) and the form of sensitivity analysis used?
9.3 Were the conclusions of the study sensitive to the uncertainty in the results, as quantified by the statistical or sensitivity analysis or both?

10 Did the presentation and discussion of study results include all issues of concern to users?

10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g., cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?

10.2 Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?

10.3 Did the study discuss the generalizability of the results to other settings and patient/client groups?

10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g., distribution of costs and consequences, or relevant ethical issues)?

10.5 Did the study discuss issues of implementation, such as feasibility of adopting the preferred program given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programs?
Drug and Therapeutics Committee
Training Course

Session 7.
Identifying Problems
with Medicine Use
SESSION 7. IDENTIFYING PROBLEMS WITH MEDICINE USE

Purpose and Content

The purpose of session 7 is to introduce participants to methods for identifying medicine use problems in hospitals and primary care clinics. Many medicine use problems may be difficult to detect on a day-to-day basis unless they are obvious. The use of the methodologies in this session will enable Drug and Therapeutics Committee (DTC) members to evaluate the pharmaceutical distribution system more closely and discover those medicine use problems that may have a significant impact on patient care.

This training module, which is the longest session in the DTC training series, is intended to be presented over a full day and followed by session 8, “Understanding the Problems Associated with Medicine Use—Qualitative Methods.”

Objectives

After attending this session, participants will be able to—

• Describe how indicators can be used to identify medicine use problems

• Perform a prescribing indicator study on a sample of prescriptions and explain how it can be used to identify medicine use problems

• Discuss the use of aggregate data including defined daily dose (DDD) to analyze the consumption of medicines

• Perform an ABC analysis and explain how it can be used to identify medicine use problems, reduce costs, and improve efficiency in the pharmaceutical supply system

• Discuss how VEN system for setting priorities will assist the DTC in medicine selection, purchasing, and inventory management

Preparation and Materials

Read—

• “Action Programme on Essential Drugs” in How to Investigate Drug Use in Health Facilities (World Health Organization, 1993)

• Managing Drug Supply, Chapter 41, “Analyzing and Controlling Drug Expenditures”

• Managing Drug Supply, Chapter 29, “Investigating Drug Use”

• Participants’ Guide
Further Readings


Introduction

The DTC has many functions and responsibilities, including evaluation and selection of medicines for the formulary, identifying medicine use problems, and promoting strategies to improve medicine use. This session reviews the methods to identify medicine use problems in the health care system.

Inappropriate medicine use results in poor patient outcomes and wastes significant amounts of money and other resources. This problem is worldwide, especially in developing countries. The impact on the health care system of inappropriate medicine use is dramatic and can lead to—

- Reduction in the quality of pharmaceutical therapy leading to increased morbidity and mortality
- Increased cost as a result of using the wrong medicine, dose, route, or amount, and because of treatment failures
- Increased risk of unwanted effects such as adverse drug reactions (ADRs) and the emergence of antimicrobial resistance

The DTC must conduct activities to evaluate and assess medicine use in order to identify those areas that need improvement. The particular medicine problem may not become obvious until analysis of the medicine use is undertaken. Access to information about medicine use can be gained using many different methods. This session discusses the following important activities for identifying medicine use problems—

- Health care facility and hospital medicine use indicators
- Aggregate data on medicine consumption and medicine use
  - DDD
  - VEN analysis
  - ABC analysis
- In-depth investigation of medicine use
  - Prescription audit (patient record review)
  - Drug use evaluation (DUE)
  - Qualitative methods

In-depth investigations utilizing qualitative methods to understand causes of a medicine use problem will be discussed in detail in session 8, “Understanding the Problems Associated with Medicine Use—Qualitative Methods.”
Part A. Identifying Problems with Medicine Use: Indicator Studies

**Indicators for Health Care Facilities**

Medicine use indicators are intended to measure specific aspects of health provider behavior and medicine use in a hospital or health center. Indicators will provide information to health care managers concerning medicine use, prescribing habits, and important aspects of patient care. They reflect the status of an important characteristic of the given health care service.

**Characteristics of Sound Indicators**

Indicators selected to assess a health care service should be relevant, easily generated and measured, valid, consistent, reliable, representative, sensitive to change, understandable, and action oriented.

- Relevant—An indicator should reflect progress toward stated national or program goals, objectives, or standards.

- Easily generated and measured—As far as possible, data for essential indicators should result from normal service and surveillance activities, and they should be found in routine records and reports.

- Reliable—Each indicator must give consistent results over time and with different observers. If one observer reports a certain result from a set of data, it is expected that a second observer will report the same result.

- Valid—Each indicator must allow a consistent and clear interpretation and have a similar meaning across different environments.

- Action oriented—The data needed for an indicator should be useful for those doing the recording, whether they are physicians, pharmacists, nurses, or other staff; the data must lead to necessary action to improve use of medicine.

Indicator studies can serve several useful purposes. They can—

- Determine where medicine use problems exist—When an indicator study shows results that are unacceptable to the DTC, then action can be taken to rectify the situation. Change is usually accomplished by comparing health care facilities indicators to determine if they exhibit a significant difference.

- Provide a monitoring mechanism—Repeating the study over a period of a year or several years will provide reliable information concerning the use of strategies to alleviate the medicine use problem.

- Motivate health care providers to improve and follow established health care standards.
Medicine use indicators have been developed by many different organizations, hospitals, and governments to identify medicine use problems. WHO and the International Network for Rational Use of Drugs (INRUD) have developed indicators for assessing health care and medicine use for primary health care (PHC) in dispensaries, clinics, and hospitals. (See “Action Programme on Essential Drugs” in the WHO manual How to Investigate Drug Use in Health Facilities.) These indicators of medicine use (i.e., prescribing, patient care, facility, and complementary indicators) which are basic and highly standardized have been reliably used and tested over years in many different countries. They can be used in almost any country and, in the hands of trained personnel, will give reproducible results. The different types of indicators developed by WHO and INRUD are described in the sections below.

**Core Medicine Use Indicators**

- **Prescribing indicators**
  - Average number of medicines per encounter
  - Percentage of medicines prescribed by generic name
  - Percentage of encounters with an antibiotic prescribed
  - Percentage of encounters with an injection prescribed
  - Percentage of medicines prescribed from an essential medicines list (EML) or formulary

- **Patient care indicators**
  - Average consultation time
  - Average dispensing time
  - Percentage of medicines actually dispensed
  - Percentage of medicines adequately labeled
  - Percentage of patients who know how to take their medicines

- **Health facility indicators**
  - Availability of EML or formulary to practitioners
  - Availability of a key set of indicator medicines
  - Availability of standard treatment guidelines (STGs)

**Complementary Medicine Use Indicators**

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

These indicators represent a small number of core indicators that have been successfully used. Other indicators can be added as needed to be more complete, but they may not have been tested for reliability as these have. Results with these indicators should point to particular medicine use
problems that need further examination in more detail and ultimately a plan to resolve the problem by the DTC.

Performing an indicator study involves planning, logistics, time, and funding. The indicator study will involve—

- Determining objectives, priorities of the study, indicators, and indicator recording forms
- Determining study design according to objectives
  - Monitoring over time and comparing facilities (cross-sectional survey, time series)
  - Evaluation of interventions (randomized controlled trial)
- Defining indicators and data collection procedures
- Pilot-testing the procedures
- Training data collectors
- Randomly selecting facilities in the region from which to collect data
- Obtaining data from approximately 30 medicine use encounters for each facility
- Analyzing data
- Providing results to the DTC for evaluation and follow-up

Typically, researchers collect medicine use data from a sample of health facilities in a region or district. The number of health care facilities from which to obtain data varies but should include at least 20 facilities with 30 prescriptions for each facility. This number would give a total sample of at least 600 prescriptions for applying the indicators to evaluate medicine use. If the objective is to perform the indicator study in one facility, at least 100 prescriptions should be collected per facility or per prescriber at any given time. It is important to perform the study in a time-series format (e.g., every quarter), so the DTC can monitor the prescribing patterns and take appropriate action as needed periodically.

For more information on study designs, sampling, and logistics concerning a particular indicator study please refer to chapter 3 “Study Design and Sample Size” in the WHO manual, *How to Investigate Drug Use in Health Facilities*.

Data collected can be compared to local medicine use statistics, regional statistics, or international statistics. The results can be used to—

- Describe current treatment practices
- Compare the performance of individual facilities or prescribers
- Conduct periodic monitoring and supervision of specific medicine use behaviors
- Identify potential medicine use problems that affect patient care
- Assess the impact of an intervention
Once a potential problem is identified, the DTC must be prepared to formulate a strategy to correct the problem. The strategies that may be used include managerial (e.g., DUE or the use of STGs or structured ordered forms), educational (e.g., face-to-face instruction or in-service education), and regulatory interventions.

**Indicators for Hospitals**

In response to antimicrobial medicine resistance problems worldwide, Management Sciences for Health (MSH) developed a manual for assessment of antimicrobial medicine use in hospitals, *How to Investigate Antimicrobial Drug Use in Hospitals: Selected Indicators* (Management Sciences for Health 2001). As a tool for hospital managers to assess antimicrobial medicine management and use, this manual was designed to contribute to reducing antibiotic misuse.

The MSH manual is intended for use by hospital DTCs, physicians, pharmacists, and managers, as well as medicine use researchers, who want to evaluate and improve antimicrobial medicine use in hospitals. It will allow basic comparisons of antimicrobial medicine use in a hospital over time and between hospitals.

The MSH manual is divided into two sections. The first describes the indicators for antimicrobial medicine use and management according to a standard format, and the second suggests procedures to apply them in a hospital study. The following indicators that were developed are presented in the MSH manual for use by hospitals.

**Hospital indicators**

1. Existence of STGs and a set of officially sanctioned antimicrobial medicines in a formulary list
2. Availability of a key set of indicator antimicrobial medicines in the hospital stores on the day of the study
3. Average number of days that a set of key antimicrobial medicines is out of stock in a 12-month period
4. Expenditure on antimicrobial medicines as percentage of total hospital pharmaceutical costs

**Prescribing indicators**

5. Percentage of hospitalizations with one or more antimicrobial medicines prescribed
6. Average number of antimicrobial medicines prescribed per hospitalization with antimicrobial medicines prescribed
7. Percentage of antimicrobial medicines prescribed consistent with the hospital formulary list (which may or may not be a part of the national EML or formulary list)
8. Average cost of antimicrobial medicines prescribed per hospitalization with antimicrobial medicines prescribed

9. Average duration of prescribed antimicrobial pharmaceutical treatment

10. Percentage of surgical patients who received antimicrobial medicine prophylaxis

11. Percentage of patients with pneumonia who are prescribed antimicrobial medicines in accordance with STGs

12. Percentage of antimicrobials prescribed by generic name

**Patient care indicators**

13. Percentage of doses of prescribed antimicrobial medicines actually administered

14. Average duration of hospital stay of patients who receive antimicrobials

**Supplemental indicator**

15. Number of antimicrobial medicine sensitivity tests reported per hospital admission including antimicrobial treatment

Other hospital-related indicators were developed in Zimbabwe and Australia and used there to monitor, evaluate, and improve the use of medicine. These indicators were implemented by DTCs in these two countries and include the following—

- Average number of days per hospital admission
- Average number of medicines prescribed per hospital admission
- Percentage of prescribed medicines consistent with hospital formulary list
- Average medicine cost per inpatient day
- Percentage of patients with morbidity due to a preventable ADR
- Percentage of inpatient deaths due to a preventable ADR
- Percentage of patients reporting adequate post-operative pain control
- Percentage surgical patients receiving appropriate antimicrobial prophylaxis
- Average number of antimicrobial sensitivity tests per hospital admission

**Activity 1. Calculating Prescribing Indicators from Prescriptions**

Using patient prescription records provided to you, calculate the following prescribing indicators—

- Average number of medicines per encounter
- Percentage of medicines prescribed by generic name
- Percentage of encounters with an antibiotic prescribed
Session 7. Identifying Problems with Medicine Use

- Percentage of encounters with an injection prescribed
- Percentage of medicines prescribed which are from the EML or formulary list

Use worksheet 1 to record your data and calculations. (See annex 1.)

Activity 2. Calculating Patient Care Indicators from Observing Role-Play Consultations

Calculate the following patient care indicators from the participant role-play depicting a physician and pharmacist consultation.

- Average consultation time
- Average dispensing time
- Percentage of patients who knew how to take their medications

Part B. Identifying Problems with Medicine Use: Aggregate Methods

Aggregate data on medicine use can be obtained from many sources in the health care system. Procurement records, warehouse medicine records, pharmacy stock and dispensing records, ADR and medication error records, and patient medical records are all data sources that can be used to obtain a variety of information, including the following—

- Medicine consumption
- Medicine availability
- Medicine cost data for individual medicines and for medicine classes
- Most frequently used medicines
- Per capita use of specific products
- Prevalence of ADRs (from reporting forms or from chart reviews)
- Prevalence of medication errors (from error report forms)

Careful review of these records will provide the DTC with insight concerning medicine use, cost of medicines, incidence of ADRs, errors in administration and dispensing, and other data. The DTC must promptly analyze any identified problems discovered in reviewing these data and institute a strategy to remedy each problem. The following applications can be used to help analyze aggregate data to identify medicine use problems.

Defined Daily Dose

Medicine consumption in terms of cost, as used in ABC analysis, can help the DTC check whether the pharmaceutical budget is spent in the most effective way and identify problem medicines to investigate further. The analysis of medicine consumption in terms of unit quantities can help the DTC identify over- and under-use of individual medications or therapeutic groups.
The DDD methodology converts and standardizes readily available product quantity data (such as packages, tablets, injection vials, and bottles) into crude estimates of clinical exposure to medicines, such as the number of daily doses. The DDD, which is the assumed average daily maintenance dose for the medication’s main indication (it is not the actual dose prescribed), is defined globally for each medicine by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway—http://www.whocc.no/atcddd/—much of the following material has been adapted from the center’s work. The DDD is based on the average maintenance dose for adults, but it can be adjusted to study pediatric medicine use.

Medicines may differ in the number of units, milligrams in tablets or milliliters as oral or injection formulations, in a recommended dose. 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—

- DDD per 1,000 inhabitants per day, for total medicine consumption
- DDD per 100 beds per day (100 bed-day), for hospital use

For instance, if the calculations for amoxicillin show that there were 4 DDDs per 1,000 inhabitants per day in 2002, this finding suggests that on any given day, for every 1,000 persons, four 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 would suggest that, for every 100 beds in the hospital, every day two patients received 240 mg of gentamicin. The assigned DDD for amoxicillin is 1 g and that for gentamicin is 240 mg.

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 that belong to different therapeutic groups. Medicine use 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.

Keep in mind the following important points concerning 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 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 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 should be understood for a correct interpretation of the findings.
• DDDs provide a unit of measurement that is independent of price and formulation, making it possible to assess trends in medicines consumption and to perform comparisons between population groups and health care systems.

• DDDs have not been established for topical medicines, vaccines, general and local anesthetics, contrast media, and allergen extracts.

• The DDD method should be used only in settings where reliable procurement, inventory, or sales data have been recorded.

The DDD can be obtained from two sources. The official list is published periodically by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway. MSH also publishes assigned DDDs in the *International Drug Price Indicator Guide*, most recently published in 2003.
Box 1. Example of a Calculation Using DDD

<table>
<thead>
<tr>
<th>District hospital and clinics use 22.5 million tablets yearly of captopril 25 mg and 3.0 million tablets yearly of captopril 50 mg. This medicine usage is for a population of 2.7 million people.</th>
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</table>

Calculating the consumption of captopril utilizing DDD methodology would be as follows—

Quantity of medicine used in 1 year multiplied by the strength of the product

\[(22.5 \text{ million} \times 25 \text{ mg}) + (3.0 \text{ million} \times 50 \text{ mg}) = 7.125 \text{ million mg} \text{ (total quantity consumed)}\]

Divide total quantity consumed by the assigned DDD for that medicine (for captopril = 50 mg)

\[7.125 \text{ million mg}/50 \text{ mg} = 14.25 \text{ million DDD}\]

Divide total quantity by 2.7 million and multiply by 1,000 (this is the population denominator for this method) to obtain the DDD/1,000 inhabitants/year (divide by 365 to obtain DDD/1,000 inhabitants/day)

\[\text{DDD/1,000 inhabitants/year} = 5,278\]
\[\text{DDD/1,000 inhabitants/day} = 14.46\]

This calculated dose could then be used to compare consumption of this medicine to other hospitals, regions, or countries. The DDD can also be used to compare consumption in the same region over extended periods of time.

**VEN Analysis**

The VEN system, in which medicines are sorted according to their health impact into vital, essential, and nonessential categories, is a well-known method to help set priorities for purchasing medicines and keeping stock. The DTC should be involved in the application of this system to the formulary by identifying the VEN class for all medicines approved for the formulary.

- “V” medicines are vital medicines—they are potentially lifesaving, have significant withdrawal side effects (making supply mandatory) or are crucial to providing basic health services.

- “E” medicines are essential medicines—they are effective against less severe but nevertheless significant forms of illness, but not absolutely vital to providing basic health care.

- “N” medicines are nonessential medicine—they are used for minor or self-limited illnesses; they may be formulary items and may be very important, but are the least important of items stocked in the health care system.

Managers can use a number of ways to decide how to focus their efforts to improve their medicine supply. In terms of medicine procurement and inventory management, one way to identify priorities is by applying the VEN system. Regardless of how well a supply system
works, there will always be more opportunities to improve the system than a DTC has time and resources to address. Therefore, the DTC and managers of pharmaceutical supply must narrow down the scope of what is manageable and what will provide the best return for their efforts.

This system helps the manager to set priorities for the selection, procurement, and use of medicines according to the potential health impact of individual medicines. The main objective is to give priority to essential, lifesaving medicines as opposed to expensive, nonessential items.

- The VEN analysis requires that managers be able to assign the medicines in inventory to a category of vital, essential, or nonessential. Assignment to the nonessential category does not mean that the medicine is no longer on the system’s formulary or EML. It indicates that the medicine may be considered a lower priority than other medicines on the list.

- VEN classification should be done on a regular basis, as the formulary or EML is updated, or as public health priorities change.

- Some people find three categories difficult and prefer to use only two categories (e.g., vital and nonessential or essential and nonessential). This preference does not matter as long as the categories used are relevant and allow for clear prioritization among medicines.

- Medicine ordering and stock monitoring should be directed at vital and essential medicines.

- Safety stocks should be higher for vital and essential items.

- VEN should be used to ensure that enough quantities of vital and essential medicines are bought first.

- Only reliable suppliers should be used for vital and essential medicines.

- Popularity of the medicine should be of minimal importance. The criteria of proven efficacy and cost-effectiveness should prevail.

The steps in conducting a VEN analysis are as follows—

1. Classify all medicines on the list as V, E, or N.

2. Analyze the N items. When possible, reduce quantities to purchase or eliminate purchases entirely.

3. Identify and limit therapeutic duplications.

4. Reconsider proposed purchased quantities.

5. Find additional funds if needed or possible.
The VEN system provides a valuable service to the health care system. No matter what the current funding is, the DTC (and procurement department) will know what the priorities are for ordering medicines.

**ABC Analysis**

ABC analysis is a method for determining and comparing medicine cost within the formulary system. The basic principles behind the ABC analysis may be applied to a variety of situations in which attention can be given to only a subset of issues or concerns.

The 80/20 rule, also known as the Pareto Principle, is based on observations made by an Italian economist, Vilfredo Pareto. It is also known as “separating the vital few from the trivial many” because for any group of things that contribute to a common effect, a relatively few contributors account for a majority of the effect.

For managers, this principle may be applied to determining which of the many potential improvement opportunities should be pursued first because they would focus their efforts on the few opportunities that would yield the greatest impact.

In terms of pharmaceutical supply, managers know that only a few inventory items account for the greatest expense or consumption. Based on the same thinking as the 80/20 rule, ABC analysis actually identifies three useful tiers for analysis: class A items are the few items that account for the highest cost, highest volume items. Taken together, they account for 70–80 percent of the value of medicines purchased or consumed; class B items comprise the next group of 15–20 percent, and class C includes low-cost or low-volume items. Managers can begin by concentrating their efforts on the relatively few class A items that will yield the greatest impact.

**Applications of ABC Analysis for a DTC**

A DTC can use the ABC analysis to—

- Measure the degree to which actual consumption reflects public health needs and morbidity
- Reduce inventory levels and costs by arranging for more frequent purchase or delivery of smaller quantities of class A items
- Seek major cost reductions by finding lower prices on class A items
- Reduce inventory of items that have limited use, but cost the system large amounts of money
- Provide information for choosing the most cost-effective alternatives and finding opportunities for therapeutic substitution
• Gather information for pharmacoeconomic analysis. ABC analysis will provide basic information for performing a cost-minimization and cost-effectiveness analysis.

Performing an ABC analysis is facilitated by the use of a spreadsheet that will perform the necessary calculations. For example, data from electronic procurement records for a particular hospital can be exported to a spreadsheet for analysis. Although a spreadsheet is not absolutely necessary, it becomes increasingly more useful as the number of line items grows and the complexity of the analysis widens.

The seven steps to perform an ABC analysis are as follows—

1. List all items purchased or consumed and enter the unit cost.
2. Enter consumption quantities for each item over a defined period (e.g., 1 year).
3. Calculate the value of consumption (using acquisition cost).
4. Sort the list in descending order by total value.
5. Calculate the percentage of total value represented by each item.
6. Calculate the cumulative percentage of the total value for each item. Beginning with the first item at the top, add the percentage to that of the item below it in the list.
7. Choose cutoff points or boundaries for A, B, and C medicines. For example—
   - Highest annual usage (accounts for 10–20 percent of items ordered and 70–80 percent of funds)
   - Moderate annual usage (accounts for 10–20 percent of items ordered and 15–20 percent of funds)
   - Lowest annual usage (accounts for 60–80 percent of items ordered and 5–10 percent of funds)

After completion of the ABC analysis, carefully evaluate the results in each class, especially class A. Data analysis will provide important information concerning medicine selection, procurement, and rational use of medicines.

**Drug Use Evaluation**

DUE (sometimes referred to as *drug utilization review*) is a method of obtaining information and identifying problems in medicine use. When developed and implemented properly, DUE will provide a mechanism to identify medicine use problems as well as provide a means to correct them. DUE can be defined as a system of ongoing, systematic, criteria-based medicine evaluations that will help ensure that medicine use is appropriate. If therapy is determined to be
inappropriate, interventions with providers or patients will be necessary to optimize pharmaceutical therapy.

A DUE can be structured so that it will assess the actual process of administering or dispensing a medicine (e.g., appropriate indications, dose, or ADRs) or for assessing the outcomes (e.g., cured infections or decreased lipid levels). Objectives of a DUE include—

- Identifying areas in which additional information and education may be needed for health care providers
- Ensuring that the pharmaceutical therapy meets current standards of care
- Creating guidelines (criteria) for appropriate medicine use
- Enhancing responsibility and accountability in the medicine use process
- Controlling medicine cost
- Promoting optimal medication therapy
- Preventing medication-related problems
- Evaluating the effectiveness of medication therapy
- Stimulating improvements in medication use

The concepts of using DUEs are discussed in more detail in session 8 (“Understanding the Problems Associated with Medicine Use—Qualitative Methods”) and session 10 (“Standard Treatment Guidelines”). Study those sessions to obtain more information concerning this method of identifying medicine use problems.

Activity 3. Performing a VEN Analysis

The DTC and pharmaceutical supply managers can use a number of ways to decide how to focus their efforts to improve medicine supply. In terms of pharmaceutical management and procurement, one way to identify priorities is by applying the VEN system. This system helps the manager to set priorities for the selection, procurement, and use of medicines according to the potential health impact of individual medicines. The main objective is to give priority to essential, lifesaving medicines as opposed to expensive, nonessential items.

The VEN analysis requires that managers be able to assign the medicines in inventory to a category of vital, essential, or nonessential. Assignment to the nonessential category does not mean that the medicine is no longer on the system’s formulary or EML list. It indicates that the medicine may be considered a lower priority than other medicines on the list.
• Form a small group to represent a pharmaceutical selection committee. Have the partially completed worksheet 2 on hand. (See annex 1.)

• Your hospital has received the new budget for the next annual procurement. It is $250,000—$46,046 less than what was used in the previous procurement presented in the ABC analysis on the worksheet.

• Apply the VEN system to the medicines listed and answer the following questions—
  o Which medicines would you assign lower priority for next year’s procurement?
  o Would you reconsider any quantities? Why?

• Select a representative from your group to present your conclusions to the larger group.

**Activity 4. Performing an ABC Analysis**

Generally, a few medicine items will account for the majority of funds used, and many other medicine items will account for a smaller fraction of funds used. ABC analysis is a simple but powerful technique that can be used to critically review how medicines are used and how funds are spent in a pharmaceutical system.

In this activity, you will conduct an ABC analysis in a stepwise approach using procurement and consumption data. These data will be valuable to the DTC because they will show how certain medicines are using larger percentages of the budget and where there may be a need for closer evaluation by the DTC.

A therapeutic category analysis is also reviewed as part of this activity but may be considered optional.

• Review the seven steps for conducting an ABC analysis and then complete worksheets 2 and 3. (See annex 1.)

• Answer the following questions—
  o How many “A” items are there? “B” items? “C” items?
  o What percentage of all items do “A” items represent? “B” items? “C” items?
  o What is the value of consumption for each category?
  o What percentage of the total consumption is represented by each category?
  o What particular product(s) may need to be reviewed more closely by the DTC because of their consumption?
Activity 5. Performing an ABC/VEN Analysis Using Participants’ Data

Using data that you have brought from your hospital, perform an ABC analysis and VEN analysis on all medicines that are available. Utilize computers available at the course or if your medicine list is short, manually perform the analysis.

Prepare a brief report on your analysis including the following—

- Number of medicines
- Top 10 medicines by value
- Number of medicines in “A” category
- List of all “V” medicine
- Recommendations concerning the formulary from this ABC/VEN analysis

Summary

An important function of a DTC is to identify medicine use problems and to implement corrective measures. Methods to obtain information about medicine use are numerous. This session has discussed a few important areas, including use of health facility and hospital antimicrobial medicine use indicators, ABC/VEN analysis, utilizing DDD, and medicine use evaluation.

Performing an indicator study is useful method to—

- Identify medicine use problems at individual patient level
- Monitor medicine use by physicians
- Evaluate the impact of interventions

Indicators include ones that are useful for the following health care areas—

- Prescribing
- Patient care
- Health care facility
- Hospitals

Other useful methods to identify medicine use problems looking at aggregate data include—

- DDD analysis
- VEN analysis
- ABC analysis
- Patient chart reviews
- DUE

Actually seeing many of the medicine use problems that may occur in a particular health care setting may be difficult. Some will always be obvious, but the vast majority will take analysis and evaluation of data before their adverse effect on patient care is revealed. This close analysis
will produce useful information on medicines and therapeutics that will need more in-depth evaluation and ultimately interventions to resolve.
Annex 1. Activity Worksheets

Worksheet 1. Prescribing Indicator Form

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## Worksheet 2. ABC/VEN Analysis—Results of Calculations and Ranking

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*USD = U.S. dollar*
Worksheet 3. ABC Analysis—Answer Sheet

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<th>Value (USD)</th>
<th>Percentage of Total Value</th>
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USD = U.S. dollar
Drug and Therapeutics Committee
Training Course

Session 8.
Understanding the Problems Associated with Medicine Use—Qualitative Methods
SESSION 8. UNDERSTANDING THE PROBLEMS ASSOCIATED WITH MEDICINE USE—QUALITATIVE METHODS

Purpose and Content

Session 8 is intended to provide information on how members of the Drug and Therapeutics Committee (DTC) can investigate the underlying reasons for medicine use problems in their health systems. The discussion covers four qualitative methods used to understand and document how factors such as knowledge, economic incentives, or attitudes and beliefs affect medicine use.

Reviewing the consequences of inappropriate medicine use emphasizes the need to investigate the reasons for health provider-patient behavior. The following examples illustrate how varied inappropriate medicine use can be—

- Prescribing too many medicines for a patient
- Prescribing the incorrect dose or wrong medicine
- Use of antibiotics for patients with viral infections
- Overuse of narcotics for patients with minor pain
- Prescribing medicines when none is needed

Once a medicine use problem has been identified, the DTC must develop a plan, including interventions, to resolve or improve the specific problem. Before planning an intervention, however, DTC members should first understand the reasons for the behavior behind the problem. The DTC can use the methods discussed in this session to identify the causes underlying the problem behavior and then recommend the most appropriate interventions.

Objectives

After attending this session, participants will be able to—

- Identify four qualitative methods to investigate medicine use and prescribing behavior
- Understand the use of the qualitative methods to identify why documented medicine use problems occur
- Design a simple qualitative instrument to investigate medicine use

Preparation and Materials

Read the Participants’ Guide.
Further Readings


Introduction

Discussion of medicines and their use occurs at the end of the patient consultation. Health professionals must be sure to give the correct medicine to the correct patient, and the patient must understand and comply with the treatment or else the expected improvement of the patient’s condition is not likely to occur.

Some examples of irrational use of medicines include—

- Prescribing medicines when the health problem is self-limiting and the patient would get better without taking any medicine (e.g., prescribing ampicillin for a patient who has a simple cold).

- Prescribing several medicines when fewer would provide the same effect (e.g. prescribing chloroquine and paracetamol when the patient has fever but does not have confirmed malaria).

- Prescribing the wrong medicine (e.g., prescribing gastrointestinal antimotility medicines for a child who has simple diarrhea when fluid replacement, such as oral rehydration solution, is indicated).

- Basic diagnostic tests are not ordered before prescribing (e.g., prescribing an expensive third-generation cephalosporin medicine when no culture has been done to ensure effectiveness of the prescribed medicine for the strain of microorganism present in the patient).

- Prescribing more expensive injections when the patient could take oral medicines (e.g., prescribing ampicillin 500 mg injection instead of the generally cheaper ampicillin 500 mg tablets).

- Wrong quantity of a medicine is dispensed to the patient (e.g., dispensing only six tablets of co-trimoxazole when the prescription is for one tablet to be taken two times daily for five days).

- Poor patient compliance because of inadequate labeling of the medicine container. Instructions on dosage frequency, for example, must be written on the container label so
the patient will have a reference point when he or she arrives home and becomes involved in other activities.

Reasons for practitioners to prescribe and dispense medicines irrationally include profit motives, lack of knowledge, and a lack of confidence in their capacity to provide quality care.

Because one of the main functions of the DTC is to identify areas where irrational use of medicines is occurring and, subsequently, to design interventions for correcting the problem behaviors, the committee needs a systematic way to collect data about medicine use.

Quantitative methods of data collection such as ABC or vital, essential, nonessential (VEN) analysis, defined daily dose (DDD) methodology, WHO health facility indicators, and hospital medicine use indicators of prescribing studies, are discussed in session 7, “Identifying Problems with Medicine Use.” Drug use evaluation, a method to identify and improve medicine use problems, is discussed in session 7 and session 11, “Drug Use Evaluation (DUE).” Those quantitative methods identify the presence of medicine use problems and their magnitude, but not necessarily why the medicine use problems are occurring.

The qualitative methods discussed in this session provide ways to target health providers, patients, provider-patient interactions, and the complex of cultural, social, economic, and structural factors that can influence behavior—thus the why of medicine use problems. The methods discussed are—

- Focus group discussions (FGDs)
- In-depth interviews
- Structured observations
- Structured questionnaires

**Key Definitions**

**Focus group discussion**—In an FGD, a small number (6–10) of people who share similar characteristics such as age, gender, or type of work are brought together by the researchers for a discussion. A trained moderator encourages participants to reveal underlying opinions, attitudes, and reasons for the problem being studied. The discussion is recorded and analyzed systematically to identify key themes and issues. This method will identify a wide range of beliefs and opinions.

**In-depth interview**—An in-depth interview allows extended discussion between a respondent and an interviewer. The interview is flexible and often unstructured, allowing an interviewer to encourage the respondent to talk at length about a particular topic of interest.

**Structured observation**—The structured observation study method utilizes trained people to observe a series of encounters between health providers and patients. The observers record the behaviors and impressions they witness during the encounters, or depending on the design of the
study, they record a score for each observed interaction on a set of indicators prepared for the study.

**Structured questionnaire**—The structured questionnaire involves the preparation of a list of questions with a fixed set of responses or options to collect the desired information in a standard way from all respondents. The questionnaire may be administered by an interviewer or completed alone by respondents. This method identifies the frequency of beliefs and opinions of the targeted practitioners.

**Applying Qualitative Methods to Medicine Use Studies**

Before establishing a procedure to correct an identified medicine use problem, the DTC should determine why prescribers and patients act as they do, thus giving insight into how their inappropriate medicine use behavior can be changed. The following are a few examples of ways the qualitative methods can be used in a health system. They—

- Complement a quantitative study
- Collect data to explore a topic about which little is known
- Provide background data before developing the training materials for a planned educational intervention and for developing managerial and regulatory interventions

As an example of the use of qualitative methods, prescribing by brand name was very popular at the district hospital. Despite numerous interventions including face-to-face discussions, in-service education, policy and procedures changes, physicians continued to prescribe by brand name. Using qualitative methods, investigators discovered that physicians were receiving educational “benefits” from pharmaceutical companies in exchange for their prescribing of branded products. This problem was then corrected once the reasons for the medicine use behavior became known. Some other factors that have an influence on medicine use—

- Personal—including acquired habits and cultural beliefs
- Interpersonal—as they relate to patient demand
- Work group and work place—including infrastructure, authority and supervision, relations with peers, workload issues
- Informational—issues include unbiased information especially from the pharmaceutical industry
Qualitative Methods

Focus Group Discussions

The FGD technique can be used by a DTC to identify a range of beliefs, opinions, and motives of a target group. The following are some characteristics of the technique.

Participants

The makeup of the study group will depend on the medicine use problem under investigation. A focus group is normally small, with 6 to 10 participants. Random selection of participants is not necessary, as is the case with other types of studies. Instead, the study investigator selects those participants who have the potential to provide meaningful information about the study topics.

Locale

The group meets in an informal location so participants will feel relaxed and can openly discuss their opinions about the subject matter.

Number of Discussion Groups and Sessions

The number of discussion groups and group sessions varies with the nature of the study population and its social characteristics. The general rule is to conduct as many FGDs with the target groups as necessary to answer the medicine use study questions. If the study population is varied, generally two to four discussions could be held for each significant target group. One discussion for a study topic in a certain target group is rarely sufficient. When placing participants in a certain discussion group, consider group dynamics and avoid combinations in which one person might be inhibited by another’s official status within the health system, for example, health workers grouped with hospital directors, nurses, and physicians.

Moderator and Recorder

A group moderator guides the discussion to keep it focused and encourages in-depth expressions of feelings and opinions on the selected topics by all participants. The moderator must be careful not to take over the group, but should instead elicit participant responses.

The group recorder’s responsibility is to record the verbal and nonverbal expressions during the sessions for later reference. Recording may be done with a tape recorder, video, or laptop computer, or it may be done manually. Generally, the recorder does not participate in the discussion.

Advantages and Disadvantages

The FGD method is advantageous in that it is relatively inexpensive to conduct and can be organized in a short time. Discussion sessions often last as little as two hours. Discussions can identify a range of beliefs and ideas.
Disadvantages of the method are that the groups may not represent the larger target population, since participants are not chosen randomly. Furthermore, a successful outcome largely depends on the skills of the moderator, who can allow bias of participant responses to influence the study when expressions or feelings are exaggerated or can allow the discussion to be dominated by a few stronger willed participants.

**In-depth Interviews**

The in-depth interview technique can be used by a DTC to expand the results of a quantitative study by exploring the reasons persons responsible for medicine use problems do what they do or to evaluate the impact of a medicine use intervention implemented by the committee. The following are some characteristics of the technique.

**Participants**

The in-depth interview is conducted individually, that is, only one respondent and one interviewer are present at the time of the session. Participants are not selected randomly, but rather are selected based on their position in the health system, where their attitudes, beliefs, and knowledge are expected to be similar to that of the bigger target population or group.

**Number of Interviews**

The number of interviews to conduct depends on the diversity of the target population. Five to 10 in-depth interviews for each important target group are sufficient. During an interview, 10 to 20 topics related to the medicine use problems under study may be covered.

**Interview Session and Interviewer**

The session is conducted using predefined but open-ended topics. This technique allows the respondent to discuss the topics as they interest him or her. The interviewer should have formal training in social science or interviewing or have substantial training and education in a health-related area such as nursing, pharmacy, or medical social work. The interviewer must also be knowledgeable about the interview topic so that he or she can expand the questioning during the interview.

**Advantages and Disadvantages**

Because it is one-on-one and uses open-ended discussion topics, the in-depth interview technique requires trust to develop between the respondent and interviewer. The interviewer can probe for more in-depth beliefs and attitudes with questions such as, “What would be your reaction if this health facility established a policy of limiting antibiotic prescribing for preoperative patients?” or “Can we talk about other medicines really needed for preoperative patients?” Another advantage of this method can be the revelation of unsought but significant data during the interview process.
Disadvantages of the in-depth interview method are that open-ended topics often generate large quantities of data, which are difficult to manage and can be time-consuming to analyze. Furthermore, unless the interviewer is well trained, the respondents may give answers they think the interviewer wants to hear or that are socially acceptable at the time, thus introducing bias into the study results.

**Structured Observations**

The structured observation method can be used by a DTC to study behaviors such as the interactions involved with patient encounters in the health system. This method is good for studying issues such as patient demand or the quality of communication between providers and patients. The data can be used as a supplement to other study methods or independently. The following are some characteristics of the technique.

**Subjects to Be Observed**

The structured observation technique involves the direct observation by trained observers of health care providers during normal patient encounter activities in normal treatment settings. The persons to be observed are determined by the number and types of health facilities designed into the medicine use study.

**Number of Observation Sites**

The number of observation sites is determined by the objectives of the study, characteristics such as the difference in patient attendance at various health facilities, and the size of population to be studied. If the study population includes a large group of health facilities, then, generally, a minimum of 10 randomly selected sites would be chosen for the study.

**Number of Observations at Each Site**

The number of observations to be conducted at each site is contingent on the objectives of the study. The investigator should plan to follow the patient all the way through the facility, from registration to consultation to pharmacy. Observing at least 30 provider-patient encounters at each site should be sufficient to describe the treatment practices.

**Advantages and Disadvantages**

Structured observations provide an excellent way to understand the complexity of behaviors that happen when persons seek medical care. Using this technique, health care providers are observed in their own environment and data collectors can gain insights that would not be possible otherwise. Another advantage is that data on actual behavior, as opposed to reported behavior, is collected.

A disadvantage of the method is the possible bias created when providers modify their normal behaviors while being observed. This bias can be minimized by skilled observers who are able to
blend into the normal practice settings and who can make providers feel comfortable in their presence. This method is not appropriate for analyzing infrequent behaviors.

**Structured Questionnaires**

The questionnaire method can be used by a DTC to quantify the frequency of attitudes, beliefs, and knowledge about medicine use. Questions can focus on factual material, such as what a respondent knows about standardized diarrhea treatment, or on a respondent’s attitudes, opinions, and beliefs about the subject matter. The following are some characteristics of the technique.

**Respondents**

Selecting the persons to include as respondents using the questionnaire technique depends largely on the target population, the study objectives, and the intended use of the study findings. For example, if the objective is to measure improper treatment of diarrhea in children younger than five years in rural hospitals, respondents from two target groups would be included—pediatric health care providers and mothers of the children.

**Number of Respondents**

The number of respondents to include in the study will depend on the objectives of the study. For example, if the goal is to simply understand the attitudes and beliefs about use of chloroquine in malaria cases, a sample of 50 to 75 respondents from each target group would be sufficient. If, however, the goal is to measure treatment gaps by providers in malaria cases, a much larger sample must be selected to increase reliability of the data collected.

**Interviewers**

The questionnaire method frequently uses the interview technique, and the interviewer should have formal training in social sciences or at least a secondary education in a health-related area such as nursing, pharmacy, or social work. Interviewers should be well trained in interviewing methodology to ensure data collection in a standardized way. Proper supervision of interviewers is essential to ensure uniformity and accuracy of process.

**Questions**

All respondents should be asked precisely the same questions. Questions may be open- or closed-ended. Open-ended questions allow the respondent to answer spontaneously, while closed-ended questioning provides a fixed set of responses from which the respondent may choose his or her answer. No leading questions should be used.

**Advantages and Disadvantages**

Because the questionnaires ask questions that are understandable and familiar to the respondents, whether they are health providers, patients, or mothers of patients, they are useful in measuring
the strength and prevalence of attitudes, beliefs, and knowledge of medicine use. Questionnaires are also useful because they can be generalized to a wider population.

One disadvantage is that structured questionnaires are not designed to uncover the unexpected. Furthermore, use of the structured questionnaire carries the risk of getting responses that are biased by what the respondent thinks the interviewer wants to hear, because responses to a questionnaire survey are very sensitive to how questions are worded. With a skilled interviewer and well-thought-out questionnaires, however, an investigator can minimize this disadvantage. A final disadvantage is that large structured questionnaire surveys are expense to conduct.

Activities

The activities included in this session allow participants to practice developing a questionnaire that could be used to obtain information on prescribers’ habits and knowledge about antibiotic use in children in their health system.

Participants will work in teams of five and select a leader to facilitate the activity. A recorder will document the questions as they are developed by the group, and the leader will present the final questions in a plenary session.

Activity 1. Deciding what questions to ask during qualitative methods to find out the reasons for high antibiotic use in your hospital

The first step to developing qualitative instruments is to decide what questions you need to ask of which people to determine why a particular medicine use problem is occurring. For this activity, assume your hospital has very high antibiotic use level, and you want to investigate this through—

- Exiting patient interviews
- Observation of the consultation
- In-depth interviews with the prescriber

Using these three methods, discuss in your groups what questions you need to answer to determine the motivations underlying the problem of high antibiotic use. You may use indirect questions and observation as well as direct questions depending on the type of instrument. After discussing in your group, you will be asked to present your findings.

Activity 2. Designing a qualitative instrument to investigate why antibiotic use is so high in a district hospital

For this activity, assume that not only is antibiotic consumption in your hospital high, but also according to a recent prescription audit, it is often inappropriate. Each group will develop one
qualitative instrument to investigate the reasons underlying this antibiotic overuse. These instruments include—

- In-depth interview with prescribers
- Structured interviews with exiting patients
- Structured observation of the consultation

Each group will prepare a role-play based on the instrument. During preparation, each group will construct their instrument on two transparent sheets for the overhead projector using capital letters of sufficient size to be seen from the farthest point of the classroom. During the role play, one group member will show the transparencies of the instrument on the overhead projector and another group member will play the role of investigator (i.e., interviewer or observer). The other roles will be played by participants selected randomly from other groups by the facilitator. The transparencies will allow other members of the class to judge your instrument more effectively.

During each role-play, everyone will need to determine the following—

- Was the instrument clear and useful?
- Did the instrument detect an underlying motive for the excessive antibiotic use?

**Activity 3. Preparing Interview Questions for Prescribers (Optional)**

Develop a questionnaire to evaluate the use of antibiotics in a health care facility. In developing the questionnaire, participants should consider the following sample elements of study design because they may impact the appropriateness of the questions and how respondents comprehend the meaning of the questions.

- Prescriber target groups—one group or several groups, such as physicians or nurses,
- Health facilities—all hospitals, specialty hospitals, outpatient departments, primary health care clinics, others
- Geographic location of facilities
- General education and training levels of prescriber target groups
- Age groups of children
- All antibiotics prescribed for the specific health problems in children

Word the actual interview questions to ensure that data will be collected on which antibiotics the prescriber normally orders for the specified health problems by age group studied, and also why the prescriber orders the antibiotics he or she does (e.g., standard or approved treatment, no time to review modern practices in the literature, or lab tests like antibiotic sensitivity not available). See a sample interview questionnaire in annex 1.
One group will be selected to interview another group using its prepared questionnaire. This role-play exercise will be useful to determine the kinds of information and problems that actually arise out of a questionnaire and interview.

**Summary**

The four study methods presented in this session provide a mechanism for the DTC to quickly assess the causes of a medicine use problem. The study methods can be used individually or to supplement quantitative survey methods, thus rounding out the committee’s understanding of medicine use behavior.

Although the methods are best implemented by social scientists, professionals in the health field, such as nurses and social workers, could be oriented and trained to design and carry out qualitative surveys.

For easy reference, the four qualitative methods are listed below with a synopsis of individual characteristics of each method.

- **Focus group discussion**
  - Less than a two-hour discussion
  - Moderator leads discussion
  - Respondents have similar characteristics such as age, gender, social status
  - Discussion topics are predefined
  - Informal, relaxed ambience
  - Reveals beliefs, opinions, and motives

- **In-depth interview**
  - One-on-one extended interview
  - Questions are predetermined and open-ended
  - Can cover up to 30 topics
  - Reveals beliefs, attitudes, and knowledge

- **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 behavior

- **Questionnaire**
  - Questions are standardized with a fixed set of responses or options
  - Respondents are selected to represent the larger population
  - Useful for a large sample of respondents
  - Measures the frequency of attitudes, beliefs, and knowledge
Annex 1. Sample Interview Questionnaire for Prescribers

1. Introduction of interviewer

2. Purpose of interview

   I know that treatment of children in our health facilities often involves prescription of antibiotics. The Drug and Therapeutics Committee is interested in knowing more about the types of antibiotics prescribed and your views about antibiotic use.

3. Respondent’s background

   What is your position in this clinic?
   Your educational background?
   Other training?
   What is your age?

4. Clinical experience

   On an average day, how many children do you treat?
   What are the most prevalent health problems of children you treat in this clinic?

5. For each type of infection you encounter in children, please explain how you treat them.

   Medicines prescribed
   Instructions to mother
   Care in clinic
   Care at home
   Other

6. When treating a child at the clinic, what factors determine whether you give an antibiotic?

   Your personal experience
   Your knowledge of peer practices
   Mothers’ expectations
   Knowledge of standard treatment guidelines for the health facility
   Use of an essential medicines list or formulary
   Results of laboratory tests

7. Where do you get medicine information to make the decision to prescribe medicines?

   None available in clinic
   Professional journals
   Clinic treatment guidelines
   Professional training in school
   Continuing education classes (What is the frequency of these classes?)
8. Closing remarks

I appreciate your time and willingness to respond to the questions. Do you have anything you would like to add to what we discussed? Are there related topics that were not covered and for which you would like to provide some information?

Thank you
Session 9.
Strategies to Improve Medicine Use—Overview
SESSION 9. STRATEGIES TO IMPROVE MEDICINE USE—OVERVIEW

Purpose and Content

Session 9 is designed to provide information on how members of the Drug and Therapeutics Committee (DTC) can apply interventions to resolve medicine use problems. Considered to be one of the most important functions of a DTC, implementing appropriate strategies to improve medicine use will affect improved health outcomes and decrease cost.

Strategies that will be discussed include the following educational, managerial, and regulatory methods—

- In-service education programs
- Pharmaceutical bulletins and newsletters
- Formulary manuals
- Face-to-face communication
- Standard treatment guidelines (STGs)
- Audit and feedback (drug use evaluations [DUEs])
- Clinical pharmacy programs
- Formulary management, including medicine selection
- Medicine restrictions and control
- Medicine registration and professional licensing

Session 9 comprises an overview of this subject; a more detailed breakdown of STGs and DUEs is provided in later sessions.

Objectives

After attending this session, participants will be able to—

- Identify effective strategies to improve medicine use based on an understanding of the factors underlying medicine use problems
- Choose an appropriate strategy for improving medicine use based on an identified problem
- Understand the importance of educational, managerial, and regulatory interventions in promoting rational use of medicines
Preparation and Materials

Read the following—

- Participants’ Guide


Key Definitions

Standard treatment guidelines (STGs)—A systematically developed collection of statements designed to assist practitioner and patient in making decisions about appropriate health care for specific clinical circumstances

Formulary manual—The document that describes medicines that are available for use in the hospital and clinics (provides information on indications, dosage, length of treatment, interactions, precautions, and contraindications)

Drug use evaluation—An ongoing, systematic, criteria-based program of medicine evaluations that will help ensure appropriate medicine use. If therapy is determined to be inappropriate, interventions with providers or patients will be necessary to optimize pharmaceutical therapy.

Introduction

As delineated in previous sessions, the DTC is responsible for numerous important pharmaceutical management functions. The DTC evaluates new medicines for the formulary, develops policies for medicine use, and identifies and corrects medicine use problems. Earlier sessions have stressed that this evaluation and addition of new medicines to the formulary is one of the most important functions of the DTC because the health care system needs medicines that are of proven efficacy for the medical conditions and diseases of the country. This efficacy must be well recognized and accepted by experts in the field. The DTC must have considerable information concerning all aspects of quality to ensure the products added to the formulary meet minimum quality standards. Evaluation of cost is essential—more important today than at any other time—because the cost of medicines as a percentage of the health care budget is increasing dramatically.

Once medicines have been added to the formulary and all of the evaluation criteria have been satisfied, then serious consideration must be given to ensuring that the medicines are used appropriately by the health care system. Session 9 concentrates on strategies for improving medicine use in the health care system.
Like the functions of evaluating medicines and adding them to the formulary, DTC’s function of ensuring proper use of selected medicines is important to the overall management of medicines: the inappropriate use of medicines will compromise any advantages achieved by proper selection. These complementary issues—selecting an appropriate medicine and then ensuring its appropriate use—lie at the very heart of pharmaceutical management. Consequences of irrational medicine use include the following—

- Increased morbidity and mortality
- Waste of resource
- Increased incidence of adverse drug reactions
- Antimicrobial resistance through misuse and overuse
- Increased infectious diseases due to contaminated and unnecessary injections

Session 9 provides the participants with insights into developing and implementing strategies to improve medicine use. Three types of strategies will ensure the quality of pharmaceutical therapy: educational, managerial, and regulatory. These strategies are discussed in detail and provide information to the participants to improve rational use of medicines.

**Educational Methods for Improving Medicine Use**

The DTC must be involved in educational programs for health care professionals. Physicians, nurses, pharmacists, and, indeed, all professionals need constant updating of their skills and knowledge. It is not possible for physicians or pharmacists to keep up with the constant changes in the pharmaceutical literature without intensive efforts by the individual and the health care system.

Educational methods are intended to inform and persuade practitioners and include the following—

- Printed materials
  - Pharmaceutical bulletins and newsletters
  - Formulary manuals and STGs
- Face-to-face communications with physicians, health care leaders, and patients

**Pharmaceutical Bulletins and Newsletters**

Pharmaceutical newsletters can be a valuable instrument for the DTC in providing medicine information. These newsletters, which can be published monthly, quarterly, or at longer intervals, should provide interested staff with unbiased and accurate information concerning pharmaceutical therapy. Newsletters and bulletins have an advantage over formal group presentations because busy practitioners can read the information on their own schedules.

Numerous pharmaceutical newsletters and bulletins are already published by international services and distributed worldwide, but a local bulletin would also be an invaluable asset. A local
 bulletin would provide more information concerning medicines and medicine-related problems of interest at the local level.

Pharmaceutical newsletters are more likely to be effective in improving use of medicines if they do the following—

- Describe the reasons for prescribing behavior—inadequate training in infectious diseases? Distrust of in-country medicines? Reliance on brand name medicines and distrust of generics?
- Offer concise, up-to-date information that can be used immediately
- Provide limited information and repetition of key points in the newsletter—extensive presentations of new information and reviews will not hold the interest of most individuals.
- Provide a graphical, colorful newsletter that will catch the attention of the reader
- Provide reference in the newsletter to information derived from reputable journals and services
- Provide brief, straightforward text
- Provide information oriented toward actions and decisions
- Obtain feedback from the professional staff on the value of the newsletter and institute changes as necessary

**Formulary Manuals and STGs**

The use of a formulary manual has been shown to be valuable in providing medicine information to physicians, pharmacists, and nurses. A formulary manual can be described as the publication dedicated to presenting the formulary list and other information concerning the use of medicines. The formulary manual is a concise, pocket-sized document that provides summary information meant to be readily available for health professionals to use daily. Formulary manuals vary in scope from a listing of essential medicines to comprehensive references that contain medicine information, treatment guidelines, and pharmacy policies and procedures. The following are some examples of content for a formulary manual—

- Medicine formulary list
- Basic information on each medicine (i.e., indications, dose, side effects)
- Supplementary information on each medicine (i.e., price, source of supply)
- Prescribing and dispensing guidelines
- Disease management guidelines for selected conditions
- Pharmacy policies and procedures pertinent to medical staff and pharmacy
- Pharmaceutical procurement policies
Ideally, the manual should have at a minimum the list of formulary medicines and an information section describing each medicine. This manual, when provided in a comprehensive form, provides excellent medicine information for physicians and other professionals. Producing the manual is a time-consuming process and a systematic participatory approach is required to keep revisions updated. See session 2, “Developing and Maintaining a Formulary,” for more detailed information concerning formulary manuals and their content.

STGs serve as evidenced-based reference guides for education of providers and for prescription audit. These documents list the preferred pharmaceutical and nonpharmaceutical treatments approved for a particular health care institution. See session 10, “Standard Treatment Guidelines,” and the “Standard Treatment Guidelines” section below for more information about STGs.

**Face-to-Face Communications**

*In-service Education Programs, Workshops, and Seminars*

The information database on medicines and pharmaceutical therapy is constantly changing. A physician or pharmacist who has recently graduated from a training program will find that his or her knowledge base becomes inadequate in a remarkably short period. Since good patient care requires the professional to have up-to-date information, in-service education and other educational programs are necessary. The DTC should have a plan to provide these programs at times when as many of the professional staff as possible can attend.

This type of information program has varying degrees of success, depending largely on the materials being presented, the style of presentation, and the education and experience of the instructor. Key points concerning face-to-face communications include the following—

- Focuses on information of local relevance
- Is kept brief (a few clear messages and instructions on what to do)
- Supplies the repetitive information needed for individuals to learn
- Is run by a presenter who has in-depth knowledge and interest in the subject and the materials presented and who has an effective teaching style

*Educational Outreach (Person-to-Person or Academic Detailing)*

Person-to-person education is the most effective educational method of changing prescribing behavior. The beneficial effects can be striking because people will be more attentive and absorb more information with this type of education. The world’s pharmaceutical companies have shown this technique to be extremely useful; they have hired thousands of representatives to meet face to face with prescribers to provide information and market their products. Pharmaceutical representatives have been remarkably successful. Academic detailing can accomplish the same result but brings a more balanced, objective message.
Principles of this type of education include the following—

- 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

**Influencing Opinion Leaders**

The identification of health care leaders and other influential persons involved in prescribing medicines and then providing education, guidance, and policies to them can have important benefits. These leaders of the health care system may well be in a position to teach or direct other doctors, students, and pharmacists on the appropriate standards of care.

A study in the United States described an intervention which targeted authoritative senior department members on the issue of antibiotic prophylaxis of caesarian sections. The intervention involved developing guidelines, which were presented to leaders in the department of obstetrics and gynecology in a hospital. These department leaders ensured through various means that the desired antibiotic cefazolin was used rather than cefoxitin. Although both antibiotics were available, a dramatic change in usage patterns occurred (figure 1).

![Figure 1. Effects of opinion leaders on the choice of antibiotic for prophylaxis in a teaching hospital.](image-url)
**Patient Education**

Patient education is a vital concept that will influence medicine prescribing. Providing regular patient education by physicians, nurses, and pharmacists will teach patients appropriate therapy and improve health outcomes. An educated patient population will make fewer demands for inappropriate medicines, especially antibiotics. Patient education will result in a corresponding improvement in how patients perceive pharmaceutical therapy and compliance with their medicine regimens.

A study from Indonesia demonstrated that moderated group discussions between community members and health workers, where both feelings about injections and scientific information about their risks were discussed, were effective in reducing the rate of injection use in public health facilities (Hadiyono et al. 1996 *Social Science Medicine*). The findings from this study in Indonesia (figure 2) are described below.

![Image showing the impact of patient-provider discussion groups on injection use in public health care facilities in Indonesia.](image)

**Figure 2. Impact of patient-provider discussion groups on injection use in public health care facilities in Indonesia.**

**Sites for Face-to-Face Education**

Persuasive face-to-face education is a flexible strategy that can occur in any setting where educators are able to talk to prescribers (or partners), for example—

- Health centers
- Hospitals
- Pharmacies
- Universities
- Continuing education seminars held at the district level
Managerial Methods

The DTC, through its function of providing rational pharmaceutical therapy, should have a number of managerial methods in place to help ensure that medicines are used correctly. These methods include the following—

- STGs
- DUEs (audit and feedback)
- Clinical pharmacy programs
  - Monitoring of medicine use
  - Therapeutic interchange program
- Medicine and antibiotic restrictions
  - Structured order form
  - Medicine availability restrictions
  - Automatic stop orders

Standard Treatment Guidelines

STGs bring another important dimension to improving pharmaceutical therapy. When developed and implemented correctly, guidelines bring significant advantages to health care programs. By definition, a treatment guideline is a systematically developed statement designed to assist practitioner and patient in making decisions about appropriate health care for specific clinical circumstances.

STGs are disease-oriented, whereas formulary manuals are very much medicine-oriented documents. Both of these documents provide important information for medical, nursing, and pharmacy staff. Every effort should be made to produce both of these manuals, have them readily available for all practitioners, and update them on a regular basis to ensure accuracy of the information provided.

Establishing an STG is a lengthy process, and one that must be done methodically and completely to have a product that all practitioners are willing to accept. The following study illustrates the value of STGs.
### Table 1. A Combined Intervention Strategy in Uganda

<table>
<thead>
<tr>
<th>Group</th>
<th>% Px conforming to STG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group—no intervention</td>
<td>24.8 → 29.9% (+5.1%)</td>
</tr>
<tr>
<td>Dissemination of STG</td>
<td>24.8 → 32.3% (+7.5%)</td>
</tr>
<tr>
<td>STG plus on-site training in therapeutic problems</td>
<td>24.0 → 52.0% (+28.0%)</td>
</tr>
<tr>
<td>STG plus on-site training in therapeutic problems plus four supervisory visits in six months</td>
<td>21.4 → 55.2% (+33.8%)</td>
</tr>
</tbody>
</table>


See session 10, “Standard Treatment Guidelines,” for more detailed information concerning advantages, disadvantages, and the process of developing this important document.

### Audit and Feedback

Audit and feedback is a managerial strategy that has been found to be successful in changing medicine use behavior. This strategy involves the monitoring of medicine use and then giving feedback on the information collected to prescribers to change medicine use behavior. This audit and feedback methodology is ideally suited for the DTC.

One type of audit and feedback program is the DUE, an ongoing, systematic, criteria-based program that will ultimately help ensure appropriate medicine use. DUEs are useful for identifying medicine use problems as well as providing an intervention method to resolve these problems. A DUE can be structured so that it will assess the actual process of administering or dispensing a medicine (i.e., appropriate indications and dose) and assess the outcomes (e.g., cured infections, decreased lipid levels).

A system of DUEs can be established in a short period once the actual medicine use problems have been identified. Many of these problems can be identified from activities described in session 7, “Identifying Problems with Medicine Use,” and session 8, “Understanding the Problems Associated with Medicine Use—Qualitative Methods.” Regular meetings of the DTC and assessments of quality measurements in the health care system should be able to identify problems that can be addressed in a DUE for resolution.

DUE should be an ongoing process during which medicine-related problems are regularly addressed. DUE must be considered a long-term program, one that is continuously updated and revised to reflect current situations and needs within the health care institution.

DUEs are discussed in more detail in session 11, “Drug Use Evaluation (DUE).”
Clinical Pharmacy Programs

The use of clinically oriented pharmacy personnel to help achieve rational use of medicines is an important intervention, one that is frequently overlooked in many countries. A well-trained pharmacist will have the skills to monitor, evaluate, and make recommendations on the use of medicines. These skills should be used as much as possible to improve pharmaceutical therapy. Pharmacists have been shown to contribute to improved care when they are involved on medical ward rounds. Studies have shown this practice to be a valuable addition to improving the use of medications in a hospital.

These individuals can be expected to ensure that indications for use are appropriate; that correct doses are prescribed, medicine interactions, and adverse drug reactions are avoided or minimized; and that patient counseling and education is provided. Pharmacy personnel can supply medical providers with up-to-date, unbiased information to help with difficult pharmaceutical therapy decisions. Pharmacists with medicine information skills should be members of the DTC. Where skills may not be available to provide some of these services, it is advisable to provide training because availability of these skills has been shown to be cost-effective in improving pharmaceutical therapy and in decreasing adverse events.

An important part of a pharmacy program is to control the use of certain medications by providing generic substitution and therapeutic substitution (interchange). In these programs, pharmacists are authorized to substitute a medicine that has been prescribed by a physician with a medicine that is considered to be equivalent. The DTC and medical staff must approve of any medicines that are a part of a therapeutic substitution scheme.

Generic substitution can be defined as the dispensing of a product that is generically equivalent to the prescribed product (i.e., having the same active ingredients in the same dosage form) and that is identical in strength, concentration, and route of administration. Considering the wide range of generic products available on the market and the significant difference in the price and quality of brands compared to generics, substitution is an efficient use of resources and can result in significant savings and improved quality.

Controversy about generic prescribing and substitution centers around bioavailability and bioequivalence of the different generic products, especially if the procurement department uses multisource products. Bioavailability refers to the speed and the extent of absorption of a medicine’s active ingredient in the blood stream. Although bioavailability is unlikely to vary significantly between most brand name and generic products (if purchasing is done through reliable, registered, and prequalified suppliers), acknowledging clinically important bioavailability problems with generic products, where they exist, is important. Several important medicines may have bioavailability issues, including digoxin, phenytoin, warfarin, rifampicin, and others. See session 5, “Pharmaceutical Quality Assurance,” for more information on this topic.

Therapeutic substitution (interchange) programs allow substitution or interchange of approved products that may differ in active ingredients, but have similar therapeutic activity in terms of efficacy and safety (e.g., lisinopril substituted for enalapril). Therapeutic substitution is
especially helpful when newer, expensive, patented, or single-source medicines are prescribed. This program can be beneficial when inappropriate prescribing of a specific medicine has been found and a suitable available alternative is comparable in efficacy and safety. As stated above, the DTC (and medical staff) must approve of any medicines that are a part of a therapeutic substitution scheme.

**Medicine Restrictions**

Many medicines, especially antibiotics, are misused, creating the need to apply restrictions on availability and use. Some common types of restrictions and controls follow.

**Formularies and Procurement Lists**

The most common method to restrict medicine availability is by use of an approved formulary or by use of a restricted procurement list. These lists are especially useful for limiting the number of antibiotics, which can become excessive if many providers and prescribers choose many different antibiotics and have many different brand preferences. Formularies can also restrict the use of medicines by limiting the number and types of medicine that will be made available at each level of health care.

Formulary management and medicine selection are discussed in detail in session 2, “Developing and Maintaining a Formulary,” and session 3, “Assessing Medicine Efficacy.”

**Structured Order Forms**

Another method of medicine restriction is the use of a structured order form that requires certain antibiotics to be prescribed (as listed on the form) for certain indications only. These forms may also have preprinted doses and dose intervals. This method has been successful for controlling medicine use in some hospitals.

**Automatic Stop Orders**

Automatic stop orders are useful for hospitalized patients and enforce restrictions on the duration of medicine use. This method has been found to provide valuable controls on the extended use of medicines, especially antibiotics and narcotics. It is a common problem for patients to be left on antibiotics for a long period because physicians have neglected to discontinue the medicine.
Control of Medical Representatives and Other Pharmaceutical Promotion Activities

Within the administrative area of the committee, the DTC must play a role in the management of pharmaceutical company representatives and promotion of medicines. Medical representatives may promote their products with biased or inaccurate information. All promotional claims should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation, and in good taste. The World Health Organization’s ethical criteria for medicinal pharmaceutical promotion

http://www.who.int/medicinedocs/index.fcgi?sid=Uj66OJ7y9ee80ca7000000004749ef6f&a=d&c=medicinedocs&cl=search&d=Jwhozip08e.5#Jwhozip08e.5

and

http://www.who.int/medicinedocs/index.fcgi?sid=Uj66OJ7y9ee80ca7000000004749ef6f&a=d&c=medicinedocs&d=Jwhozip08e.1#Jwhozip08e.1

can serve as a basis to develop measures and guidelines on pharmaceutical promotion that can be used in hospitals.

Avoiding Perverse Financial Incentives Medicine

Perverse financial incentives must always be avoided. The way hospitals and health facilities charge for medicines, particularly for outpatients and pharmacies, may affect the way they are used. Such examples of adverse promotion include—

- The promotion of overuse (including the use of expensive medicines where cheaper one would be just as good) and polypharmacy where prescribers earn part of their income from the sales of medicines

- The promotion of polypharmacy where the patient must pay the same fee or fixed charge regardless of the number and quantity of medicines they receive (e.g., a registration fee covering all medicines)

The DTC has a role in advising the hospital management or other health authority concerning these issues. If possible, agreement should be established that none of the prescribers has a direct financial interest in the health facility pharmacy.
An example of the effects of different kinds of user fees is illustrated below.

**Table 2. The Effects of Different Kinds of User Fees in Nepal**

<table>
<thead>
<tr>
<th>Group</th>
<th>Control flat prescription fee</th>
<th>1-band fee per pharmaceutical item</th>
<th>2-band fee per pharmaceutical item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of pharmaceutical items per prescription</td>
<td>2.9 (0%)</td>
<td>2.9 (–31%)</td>
<td>2.8 (–21%)</td>
</tr>
<tr>
<td>Percentage of prescriptions conforming to STGs</td>
<td>23.5 (+2.8%)</td>
<td>31.5 (+31.5%)</td>
<td>31.2 (+16.5%)</td>
</tr>
<tr>
<td>Average cost per prescription (Nepali rupees)</td>
<td>24.3 (+36%)</td>
<td>27.7 (+1%)</td>
<td>25.6 (–6%)</td>
</tr>
</tbody>
</table>


**Regulatory Methods**

Influencing appropriate medicine use through regulatory or statutory requirements is an important factor in promoting rational use of medicines.

**Pharmaceutical Registration**

Pharmaceutical registration, when enforced properly, places restrictions on medicines imported into the country. Registration keeps ineffective, poor-quality, and dangerous medicines out of the country and, thus, off the market. Monitoring and enforcement of the system is important because of the possibility of a large number of medicines reaching the public and private health care systems and private nonmedical medicine sellers or distributors. DTCs should ensure that only registered medicines are procured and used within the hospital and primary care clinics.

**Professional Licensing**

Licensing of health care professionals is a common practice that restricts the membership of the health care staff to individuals who are at least minimally competent and have necessary training and experience. Licensing can be extended to include level-of-use prescribing. This regulatory method places restrictions on the types of medicines that providers can prescribe depending on their training. These restrictions are necessary to limit untrained or minimally trained individuals to the appropriate level of clinical practice in the health care system.

DTCs should ensure that only licensed health care professionals are employed and that their duties comply with national regulations concerning their level of prescribing privileges.
Licensing of Pharmaceutical Outlets

Licensing of pharmaceutical outlets restricts the distribution of medicines to limited and qualified distributors and retailers in a country. Although difficult to enforce, it does provide the basis for which an individual or company can legally distribute prescription and nonprescription medicines. DTCs should make every effort to ensure that pharmacies are licensed and all medicines are purchased from these facilities.

Regulation of Pharmaceutical Promotion

Regulating pharmaceutical promotion activities at the national level can augment local efforts at controlling biased promotion of medicines and medical supplies. These regulations can be invaluable in controlling inappropriate use of many pharmaceuticals.

Choosing an Intervention

Choosing an intervention depends on the type of medicine use problem and the reasons it exists. Studies have shown the following—

- A single educational strategy is usually not very effective and the impact is not sustainable.
- The use of printed materials alone is not effective or advisable.
- A combination of strategies always produces better results than a single strategy.
- Focused, small groups and face-to-face interactive workshops have been shown to be effective.
- Monitoring and feedback and peer review are effective strategies to improve medicine use.
- Economic strategies are powerful strategies to change medicine use, but may be difficult to introduce.
- Treatment guidelines are effective when used with other interventions.

The most effective interventions often combine different aspects of educational, managerial, and regulatory strategies to achieve maximum impact. These strategies can be implemented together to achieve maximum impact at a single point in time, or in sequence to reinforce effects. A recent series of interventions by a group in Mexico City aimed at improving the treatment of diarrhea offers a good example of how interventions can combine different approaches (Gutierrez et al., 1993; Munoz et al., 1993).
In the initial intervention, a prescribing survey for diarrhea was carried out in two Social Security clinics in Mexico City. Physicians from the clinics then participated in a training workshop led by local “experts” where the results of the survey were presented and the physicians developed a normative treatment algorithm for diarrhea. This workshop was followed for the next six months by a peer review committee activity in which physicians from the clinics rotated through the review committee assessing their own and their colleagues’ diarrhea case records. One remarkable feature of this study is the long follow-up period (18 months), which showed how each strategy reinforced the changes in practice and how well the changes were retained (figure 3).

In subsequent work, the intervention was simplified to allow for greater dissemination (results in table 1). In the second phase, the training workshops to review the normative treatment algorithms were conducted by “opinion leaders” in 18 Mexico City clinics, rather than by experts, and there were no post-training peer review committees. In this phase, the observed pre/post increase in use of the diarrhea treatment algorithm was 25.6 percent (from 17.7 to 43.4 percent), compared to 46.7 percent (24.5 to 71.2 percent) in the initial study. In the final phase of the work, rather than conducting the intensive participatory workshops to review the treatment algorithm, the algorithm was simply taught to health staff in 124 clinics around the state of Tlaxcala by “coordinators” from the project. Following this training, use of the algorithm improved by 6.5 percent (from 24.7 to 31.2 percent).
Table 3. Impact of Training on the Use of Diarrhea Treatment Algorithm in Three Mexico Settings

<table>
<thead>
<tr>
<th>Intervention Given by</th>
<th>Prescribers</th>
<th>Baseline (%)</th>
<th>Post (%)</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experts in two clinics</td>
<td>31</td>
<td>24.5</td>
<td>71.2</td>
<td>+46.7</td>
</tr>
<tr>
<td>Leaders in 18 clinics</td>
<td>65</td>
<td>17.7</td>
<td>43.4</td>
<td>+25.6</td>
</tr>
<tr>
<td>Coordinators in 124 clinics</td>
<td>157</td>
<td>24.7</td>
<td>31.2</td>
<td>+6.5</td>
</tr>
</tbody>
</table>

This sequence of studies illustrates the magnitude of additional impacts that are possible by combining intervention strategies, but also demonstrates that even relatively limited intervention strategies can result in substantial improvements in practice.

A systematic review of published and unpublished intervention studies to promote rational use of medicines in developing and transitional countries was presented at the first International Conference on Improving the Use of Medicines in 1997. More than 30 studies of acceptable study design (i.e., randomized controlled trial, pre/post with control, or time series study) were found. The studies were grouped by category of intervention and the magnitude of impact was assessed in terms of percentage improvement in a medicine use outcome. The results are shown in figure 4 (which includes an extra category on economic strategies not originally shown in materials from the International Conference on Improving the Use of Medicines 1997).

Figure 4 illustrates that printed educational materials had little impact on medicine use, which improved by 0 to 10 percent. The impact of training programs varied between small and large, depending probably on the quality of the training. Interventions involving group process, supervision and audit, pharmaceutical supply and management, or economics incentives consistently had moderate to large impact.
Activity 1. Case Study: Generic and Brand Name Antibiotics

For this activity, assume that your DTC has noticed an increased use of certain brand name antibiotics for treating adult infections in the outpatient clinic. Less expensive generic products have recently been out of stock, but are now available. Health care providers are reluctant to use the generic products because of a lack of confidence in their quality.

The STGs for these infections are available but are not specific and therefore allow for a wide selection of different antibiotics. The costs of the brand name medicines are approximately 50 percent higher than similar generic medicines available on the formulary. Most physicians and pharmacists agree that the brand name products seem to work better and that patients are less likely to return to the clinic for follow-up visits.

The hospital has significant budget problems and the administration is looking for ways to decrease cost without compromising quality. The administration has also had many patient complaints about poor-quality medicines, especially generic products.

- What are the major pharmaceutical management problems in this case presentation?
- Clearly define the beliefs and motivations of the prescribers that may contribute to the observed behavior.
- Once the problem has been defined, what kinds of strategies or interventions would you use to improve pharmaceutical therapy in this hospital and lower medicine cost?
Summary

Session 9 provides information on strategies to improve medicine use—one of the DTC’s many functions. These programs are needed because irrational use of medicines will reverse any advantages gained in providing other DTC functions.

Important strategies to improve medicine use include—

- Educational programs
  - In-service education programs
  - Pharmaceutical bulletins and newsletters
  - Formulary manuals
  - Face-to-face discussions

- Managerial programs
  - DUEs
  - STGs
  - Clinical pharmacy programs
  - Medicines restrictions and control
  - Formulary list, structured order forms, automatic stop orders, and control of medical representatives and other pharmaceutical promotion activities

- Regulatory programs
  - Medicine registration
  - Professional licensing
  - Licensing of medicine outlets

Each of these areas should be addressed carefully for a successful DTC and for a successful pharmaceutical management program.
Drug and Therapeutics Committee
Training Course

Session 10.
Standard Treatment Guidelines
SESSION 10. STANDARD TREATMENT GUIDELINES

Acknowledgment

This session is based on the World Health Organization and the International Network for Rational Use of Drugs. Promoting Rational Drug Use—Standard Treatments (PowerPoint and Study Guides). http://mednet3.who.int/prduc/rduc/TOC.htm

Purpose and Content

Experience has shown that even when pharmaceutical supply is based on an approved formulary or essential medicines list, ample opportunity exists for ineffective, unsafe, or wasteful prescribing. Standard treatment guidelines (STGs) list the preferred pharmaceutical and nonpharmaceutical treatments for common health problems experienced by people in a specific health system. As such, they represent one approach to promoting therapeutic effective and economically efficient prescribing.

When implemented effectively, an STG offers advantages to patients (e.g., it provides more consistency and treatment efficacy), providers (e.g., it gives an expert consensus, quality of care standard, and basis for monitoring), supply managers (e.g., it makes demand more predictable and allows for prepackaging), and health policy makers (e.g., it provides focus for therapeutic integration of special programs and promotes efficient use of funds). Effective implementation, however, is perhaps the greatest challenge in introducing STGs.

Objectives

After attending this session, participants will be able to—

- Understand the importance of an STG in promoting rational use of medicines
- Describe the implementation of a guideline in a hospital or clinic
- Develop an STG for a disease or medical condition

Preparation and Materials

Read the following—

- Participants’ Guide
Key Definition

**Standard treatment guideline**—A systematically developed statement designed to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances

Introduction

The Drug and Therapeutics Committee (DTC) is responsible for numerous important pharmaceutical management functions. The committee is responsible for evaluating new medicines for the formulary, identifying and correcting medicine use problems, assessing and controlling adverse drug reactions among other functions. Session 10 concentrates on an important strategy for improving medicine use in the health care system—STGs. Guidelines are a valuable resource in the management of pharmaceutical therapy because—

- Treatment of diseases may have many different approaches.
- Many practitioners will not remember the best method of treatment.
- Applying the most effective treatment benefits both the patient and the health care system.
- Formulary management will have only limited impact if medicines are used incorrectly.

The development and implementation of STGs is a necessary task in a health care system where numerous treatments may be available. Physicians and nonphysician providers will use their own knowledge base, training, and preconceived ideas on the treatment rationale for each patient. Frequently, this approach is effective and reasonable and results in optimal care. Just as frequently, however, it may result in less than optimal care and in fact may result in dangerous medical care, leading to poor outcomes for the patient. The use of STGs is a time-honored system that works well and improves patient outcomes.

The Need: A Solution to Therapeutic Anarchy

STGs have existed for as long as the art of healing has existed. Traditional healers developed their standard sets of cures and passed them from generation to generation. In modern medicine, however, the concept arose that more than one treatment modality may available for many medical conditions. This concept leads to confusion and, in many cases, incorrect treatment. Doctors, nurses, pharmacists, community health workers, and other health care providers learn about all of the treatments that could be used, instead of focusing on the best treatment that should be used. Casual observation, as well as more systematic study of prescribing practices, frequently reveals a pattern of tremendous diversity among prescribers in the treatment of even the most common conditions. Polypharmacy is one problem; for example, three, four, five, six, and sometimes more medicines may be prescribed for acute viral gastroenteritis, for which only
oral rehydration therapy is effective in reducing morbidity and mortality. Other common problems are making incorrect medicine choices, overdosing, underdosing, and choosing a more expensive medicine when less expensive ones would be equally or more effective.

STGs—also known as standard treatment schedules, standard treatment protocols, therapeutic guidelines, and so forth—list the preferred pharmaceutical and nonpharmaceutical treatments for common health problems experienced by people in a specific health system. Each pharmaceutical treatment should include for each health problem the name, dosage form, strength, average dose (pediatric and adult), number of doses per day, and number of days of treatment. Other information on diagnosis and advice to the patient may also be included.

STGs should consider both pharmaceutical and nonpharmaceutical treatments. Reassurance, for example, might be the proper standard treatment for a child who is shorter than other children of his or her age, but who shows a normal growth curve, shows no signs of malnutrition or chronic disease, and has shorter than average parents.

Health problems, including specific diagnoses (e.g., malaria), symptoms (e.g., headache), and preventive health services (e.g., immunizations or prenatal vitamin and mineral supplements) may also be included in the guidelines.

STGs are currently in use in parts of the United States, Europe, Latin America, Asia, Africa, and the Western Pacific. Experience shows that even the shortest essential medicine list or formulary list offers ample opportunity to misuse medicines by improper treatment of common problems. Thus, essential pharmaceutical programs are finding that the development of standard treatments is necessary for therapeutically effective and economically efficient use of medicines.

Standard treatments are used at different points of the therapeutic process. They may be used to diagnose, decide on treatment and pharmaceutical supply, and assist with adherence to the prescribed treatment. This use will more likely lead to the desired clinical outcome.

Although the advantages to using STGs are many, some disadvantages have also been encountered.

**Advantages**

The use of STGs can benefit health care providers, health care officials, supply management personnel, and patients in the following ways.

- **Health care providers**
  - Provides standardized guidance to practitioners
  - Encourages high quality care by directing practitioners to the most appropriate medicines for specific conditions
  - Encourages the best quality of care since patients are receiving optimal therapy
• Utilizes only formulary or essential medicines, so the health care system needs to provide only the medicines in the STGs

• Provides valuable assistance to all practitioners, especially to those with lower level skills

• Enables providers to concentrate on making the correct diagnosis because treatment options will be provided for them

• Health care officials

  • Provides a basis for evaluating quality of care provided by the health care professionals

  • Provides the most effective therapy in terms of quality

  • Provides a system for controlling cost by using funds more efficiently

  • Provides information for practitioners to give to patients concerning the institution’s standards of care

  • Can be a vehicle for integrating special programs (e.g., diarrhea disease control, acute respiratory infection (ARI), tuberculosis control, malaria) at the primary health care facilities using a single set of guidelines

• Supply management

  • Utilizes only formulary or essential medicines, therefore the health care system needs to provide only medicines in the STGs

  • Provides information for forecasting and ordering (because medicines and quantities for common diseases will be known)

  • Provides information for purchase of prepackaged medicines

• Patients

  • Patients receive optimal pharmaceutical therapy

  • Enables consistent and predictable treatment from all levels of providers and at all locations within the health care system

  • Allows for improved availability of medicines because of more consistent use and ordering
- Helps provide improved outcomes because patients are receiving the best treatment regimens available
- Lowers cost

**Disadvantages**

STGs have drawbacks as well—

- Inaccurate or incomplete guidelines will provide the wrong information for providers and therefore do more harm than good. Guidelines may not be based on the most reliable information.
- Developing and updating guidelines is difficult and time-consuming and must be done on a regular schedule or they will become obsolete very quickly.
- Guidelines provide a false sense of security; that is, many providers will limit their evaluation of a particular patient as soon as it fits into a particular standard treatment.

Standard treatment guidelines are disease-oriented whereas formulary manuals are medicine-oriented documents. These two documents provide the very essence of the DTC’s efforts to provide rational pharmaceutical therapy. Every effort should be made to publish both of these manuals, have them readily available for all practitioners, and update them regularly to ensure accuracy of the information provided.

**Establishing STGs**

Establishing STGs is a lengthy process, one that must be done methodically and completely to have a product that all practitioners are willing to accept. The process can be described in eight steps—

1. *Establish a committee to address the development of the guidelines.* The DTC may take responsibility for this task, or it may select individuals to form a new committee for the purpose of establishing the guidelines.

2. *Develop an overall plan for guidelines.* A comprehensive plan with well-defined time frames is necessary to ensure that the product is started and finished within a reasonable period. Select a format. Recruit contributors, writers, and reviewers.

3. *Identify the diseases that the STGs will cover.* The most common and serious diseases and medical conditions should be selected from available morbidity statistics. All of the medical departments and specialty areas should be consulted to identify important diseases to be addressed in the guidelines.
4. **Determine appropriate treatment options.** This step is critical. Evidenced-based information must used to identify appropriate treatment guidelines. Experts and clinical specialists should be consulted to confirm proposed treatment options. Guidelines must be consistent with national formularies and guidelines.

As a general rule, STGs should—

- Use the fewest medicines necessary to treat the medical condition
- Choose cost-effective treatment
- Use formulary medicines (from local and national formularies)
- Give first-, second-, and third-line treatment options, when appropriate
- Provide dose, duration, contraindications, and side effects

5. **Determine what information should be included in the STG.** Information provided in the STG can vary widely. The following elements are suggestions for comprehensive STGs.

- Clinical condition
- Diagnostic criteria and exclusions
- Treatment objectives (e.g., elimination of plasmodium parasites from a blood smear)
- Nonpharmaceutical treatment
- Medicines of choice (and alternatives) for the medical condition
- Important prescribing information—dose, duration, contraindications, side effects, warnings, medicine interactions
- Referral criteria
- Patient education information
- What to do when clinical response is poor

The amount of information to provide is a difficult decision. Ideally, the STG manual should be concise and small enough to fit into a practitioner’s pocket, but also, the STGs must be comprehensive enough to describe the medical condition and its appropriate treatment.

6. **Draft the STGs for comments and pilot testing.** STGs are controversial documents and may not be accepted by all practitioners in a hospital or clinic. The draft document must be circulated to obtain comments on the content, ease of use, presentation, and overall acceptability. This step is vital to determine future use of the guidelines and to garner buy-in from practitioners in the hospital.
7. **Publish and disseminate.** After completion and approval of the final draft, the document must be published and distributed widely to the professional staff. An official launch, training of users, and monitoring and evaluation are all necessary components to the distribution of the guidelines. This important activity is described in greater detail later in this session (see “Implementing the Guideline”).

8. **Revise and update.** Treatment recommendations change rapidly and, consequently, so must the STGs. STGs should be updated regularly to reflect changes in accepted treatment strategies. If a regular schedule for updating the STGs is not used, they will quickly lose their credibility.

Treatment guidelines must have the most up-to-date and accurate information available. Any attempt at providing a guideline without this accurate information will lead to failure of the guideline. Therefore, the use of evidence-based medicine in preparing the guideline and the use of expert authors and reviewers cannot be overemphasized.

**Key Features of a Successful STG Manual**

Seven features are key to the success of an STG.

- **Simplicity**—The number of health problems is limited. For each health problem, a few key clinical diagnostic criteria are listed. Medicine and dosage information is clear and concise.

- **Credibility**—The treatments are initially developed for patients by the most respected clinicians in the country using evidence-based information. Revisions based on actual experience will further add to the credibility. Input from paramedical staff should be actively sought and acknowledged.

- **Same standards for all levels**—Doctors and other health care providers use the same standard treatments. The referral criteria differ, but the first-choice treatment for a patient depends on the patient’s diagnosis and condition, not on the prescriber. If a patient attends a teaching hospital or a low-level dispensary with a common condition, the treatment will be exactly the same. If the patient does not respond to treatment, he or she may be referred to a higher level to receive the second-line therapy, which would be given in hospital.

- **Pharmaceutical supply based on standards**—The standard treatments are coordinated with the supply of medicines. If changed circumstances require a new medicine for the standard treatment, then the supply system must respond.

- **Introduced in preservice training**—Standard treatment manuals are distributed during preservice training and their use becomes habit.
• Dynamic (regular updates)—As bacterial resistance patterns change or other factors alter therapeutic preferences, the standards are revised to reflect current recommendations.

• Durable pocket manuals—The STGs are published as small, durable pocket manuals, which makes them convenient to carry and use.

In the interest of therapeutic and economic efficiency, standard treatments should target those conditions that have the highest morbidity and mortality rates. Note that some conditions that contribute substantially to the number of patients treated, and therefore to the total cost of medicines provided, contribute little to decreasing morbidity and mortality. Skin conditions are a common example. Such problems may nevertheless be priorities for the development of standard treatments precisely because they do absorb a large percentage of the pharmaceutical budget.

In terms of selection of health problems to be addressed, standard treatment falls into three categories—

• Individual—Standard treatments are prepared for only one problem or set of problems, such as only diarrheal disease, only ARI, or only malaria.

• Selective—Standard treatments are prepared for a small number of high-priority problems, perhaps 6 to 12, for example, a “package” of treatments for diarrheal disease, ARI, prenatal care, immunization screening, malaria, and tuberculosis.

• Comprehensive—Standard treatments are prepared for 30, 50, 100, or even more common health problems. When published, this collection of standard treatments becomes more like a textbook than a basic reference.

The number of treatment guidelines developed should be appropriate to the specific situation. But individual treatments developed one by one may miss the opportunity to use the process to integrate several special programs. At the other extreme, comprehensive standard treatments risk overwhelming health workers with new information, thus reducing the chance that any of the standard treatments—even those for common, high-priority problems—will be followed. There may be a place for targeting different levels of the health system with manuals containing differing amounts of information.

Information on local disease patterns should also be considered. Seldom do primary care clinics have access to clinical laboratories. But results from surveys using available district, regional, or national laboratory facilities can be used to make scientifically based selections of preferred medicines for certain types of diarrhea, ARI, malaria, tuberculosis, and other infectious diseases. Dynamic standard treatments are periodically updated to reflect changes in treatment patterns.

Development of standard treatments should aim at therapeutic integration through coordination with special programs such as diarrheal disease control, ARI, malaria, and so forth. Hospital or primary health care standard treatments should reinforce recommendations of special programs and, at the same time, special programs should use their experience in developing their treatment recommendations.
Individual medicine selections should, of course, be based on the principles of choosing the fewest medicines necessary to effectively treat an individual condition, choosing the most cost-effective treatment, and adhering to the essential medicines list (if one exists). If an essential medicines list does not exist for the level of health care at which the treatments will be used, then the process of producing standard treatments should also produce an essential medicines list.

Development of standard treatments must involve respected clinicians from all levels, including perhaps leading professors from local medical schools as well as experienced district medical officers and outstanding community health staff. Department heads of major hospitals should also be consulted and their advice obtained in preparing and authoring the document. Involving many end-user staff-level physicians and pharmacists is also necessary to obtain a broad-based participatory approach, one that will ensure buy-in later when the manual is completed.

Finally, the patient perspective must be considered. Issues of patient adherence to treatment (compliance) and prevailing patient preferences must be weighed against considerations of efficacy, safety, quality, and cost.

**Implementing the Guideline**

In terms of impact on prescribing and medicine use patterns, the greatest weakness in past efforts to introduce standard treatments has probably not been in *developing* reasonable standards, but in *effectively implementing* the standards once they have been developed. Prescribing patterns change slowly; consequently, practitioners must be educated in the use and importance of the guidelines. Marketing of the guideline will be crucial.

The following are important elements for a plan to implement standard treatments—

- Printed reference materials
- Official launch
- Initial training
- Reinforcement training
- Monitoring
- Supervision

Printed reference materials can include manuals, posters, and training materials. Depending on the number of treatments involved, printed references may be in the form of wall charts, pocket handbooks, or larger shelf-size reference books.

Some people feel that wall charts provide a better reminder to health workers, are more permanent, and help the patient better understand the treatment process. Others feel that a handbook is more effective, provided it fits into the pocket, is durable, and is well organized. Pocket-sized books can also include information about individual medicines or other reference data. The contents of pocket manuals can be organized in summary tables, in diagnostic and treatment decision trees or flowcharts, or simply in written text.
An official launch is important. The Minister of Health, the leaders of professional bodies, and leading clinicians should present the new guidelines at a public forum. Ideally, the presentation should be covered by the press and broadcast media and attended by representatives of health worker associations.

Initial training is also important. Ideally, standard treatments should be introduced during formal preservice training for doctors and other health care providers. Use of the standard treatments and the reference manual or wall chart early in training develops good habits for later clinical practice. It implies that examinations should include questions on standard treatments.

The length of initial in-service training will depend on the number and complexity of standard treatments. Training should specifically consider prescribers’ inhibitions about using standard treatments. Some may be afraid that looking things up in front of the patient will detract from their credibility. Participants should therefore practice the use of reference materials in actual patient care situations or in role-plays.

Other prescribers may not appreciate how the treatments were prepared and at first may not trust the treatments. Most important, if the standard treatments differ substantially from current practice (e.g., fewer injections or fewer antibiotics than currently prescribed), these differences should be identified and discussed. Participants should be strongly encouraged to accept the standard treatments, perhaps even by signing a written agreement.

Especially for health care providers already in practice, reinforcement training during the first 6 to 12 months after the initial training can play an important role in reemphasizing the importance of following standard treatments and can allow the DTC to respond to questions that have arisen from attempts to apply the treatments.

Finally, the monitoring system and supervisory efforts should focus on the priority health problems and standard treatments for these problems. Routine reports that focus on high-priority problems such as diarrheal disease and ARI can also include information on treating these problems and, of great importance, on adequacy of supply of the few medicines needed for these conditions. Using drug use evaluations (DUEs) can be helpful in monitoring and ensuring compliance with the STGs.

Activity 1. Developing a Guideline for Use during the Field Trip

For this activity, assume that your DTC has information from indicator studies, chart reviews, and ABC analysis that shows that many antimicrobial medicines are being used in excessive amounts. This overuse of antimicrobials has included treatments for pneumonia, diarrhea, and malaria and in many surgical procedures. The incidence of antimicrobial resistant malaria is also increasing in the hospital. Other indications (including many anecdotal reports) are that antimicrobials are being prescribed incorrectly, indiscriminately, and without appropriate follow-up. An ABC analysis showed that the antimicrobials account for 85 percent of the pharmacy budget.
The DTC intends to address this problem with several different strategies, including educational programs for medical providers, the institution of a DUE program for several antimicrobial medicines, and a revision of the STGs.

Meet in your usual groups and collaborate on the development of an STG for cesarean section antimicrobial prophylaxis. (If time allows, you may also be asked to develop an STG for childhood pneumonia.) Keep the guideline brief, but address all of the important aspects of care that are necessary to guide the appropriate treatment and improve patient outcomes with this disease or medical condition. Provide as well a brief workplan on how the guideline would be implemented in your hospital.

The STG that you develop in your groups will be discussed in plenary where the facilitators will help you reach a consensus between all the groups on one guideline for everyone to use. The plenary group will then develop a form to test whether patients are being treated in accordance with the guideline, and this form will be used during the field trip to a local hospital later in the course.


Designing and implementing standard treatments that truly improve prescribing practices is challenging. It requires an understanding of the issues involved in each step of the process. It also requires sufficient commitment, cooperation, financial resources, and effort.

The case study with this activity is intended to stimulate thinking and discussion about some of the critical issues in the effective introduction of STGs in a health care system.

Read the Pagalia case study (annex 1) and be prepared to discuss the following questions in your group—

- How were the Pagalia STGs developed and implemented?
- How have the treatments affected prescribing thus far?
- Should a second edition of the STGs be prepared at this time? Is it the best use of time and money?
- What should be done? What should be proposed to Mr. Domingo at the next meeting?
- What other pharmaceutical management problems exist in this case study and how would you deal with them?
Summary

STGs constitute one of the most important concepts in providing rational use of medicines. These guidelines have been shown to provide valuable guidance to practitioners at all levels, especially those with minimal training.

Guidelines need to be prepared with the ultimate goal of providing a protocol for the health care system to follow that will produce improved patient care and outcomes.

STGs will improve outcomes for patients by—

- Providing standardized guidance to practitioners
- Listing the most appropriate medicine for use
- Producing the best quality of care because patients are receiving optimal therapy
- Using only formulary or essential medicine so the system need only provide the medicine in the guideline
- Providing invaluable assistance to all practitioners, especially those with lower skill levels, as it provides the guidelines necessary to ensure good quality care
- Enabling providers to concentrate on making the correct diagnosis because treatment options will be provided for them

Annex 2 lists publications that are relevant to the development of STGs.
Annex 1. Case Study for Activity 2

A Second Edition?
Standard Treatments In Pagalia

One Morning, Mid-1998

Dr. Pedro, the Director of Health Services, sat patiently, only half listening to Dr. Karma’s animated review of the new essential medicine component of the Health Financing Project. The characteristic twinkle in Dr. Pedro’s eye remained, despite the fact that he had heard this same introduction at least twice before this month. The essential medicine component of the project was to achieve “therapeutic and economic efficiencies,” which would help the ministry make maternal and child health services more widely available and more effective.

Mr. Joko from Planning and Mrs. Soma from the Pharmaceuticals Directorate were also at the meeting along with several of their assistants. Dr. Pedro thought the assistants seemed particularly taken with Dr. Karma’s energetic presentation. “So, my friends,” Dr. Karma announced, “by next Monday we must present Mr. Domingo [the project officer for the major sponsoring donor] with a first year workplan for improving medicine use. Your thoughts, please.”

Health Status and Health Care in Pagalia

While Mr. Joko raised a few points regarding recent negotiations with the donor, Dr. Pedro reflected on the current health situation in the country. From his position in the ministry, Dr. Pedro felt he had a good grasp of needs at the health center level.

Pagalia is divided into 10 provinces and 80 districts. Health care is considered a central responsibility, so national authorities play a major role in health care policy. Pagalia’s population of over 20 million receives primary health care services from a network of nearly 300 health centers and 2,300 subcenters. In addition, nearly every district has a small hospital, and Pagalia has over 15 provincial general and specialty hospitals. UNICEF estimated that last year almost 120,000 Pagalians died—one-half of whom were under age five. The infant mortality rate is believed to have dropped below 85 deaths per 1,000 live births. As expected, the leading causes of death among the under-five age group were diarrhea disease, ARI, neonatal tetanus, measles, and other immunizable diseases. In terms of health center attendances, Mr. Joko’s staff in Planning had recently completed a study that showed ARI accounted for 36 percent of illness visits for children under age five; skin disease—17 percent; and diarrhea disease—15 percent. For adults, ARI accounted for 18 percent of attendances, skin diseases—18 percent, anemia and nutritional deficiencies—10 percent, and diarrheal disease—6 percent. Although many health centers have doctors assigned to them, a recent study from one province indicated that only about one in four patients sees a doctor. The rest are diagnosed and treated by nurses and paramedics.
Publication of the Standard Treatment

After Mr. Joko finished his questioning, Dr. Pedro began the discussion of methods to improve medicine use patterns. “The only solution is the dissemination of standard treatments. Standard treatments will straighten everything out.” He went on to describe the process which led two years ago to the publication of Standard Treatments for Health Centers.

The essential medicines list had been developed in 1991, and in 1993 concern about medicine use led to the beginning of work on standard treatments. A committee consisting of four doctors from Preventive Health Services, another person from the ministry, three people from the Faculty of Medicine, and one outside member began work in earnest on the project. In early 1996 the Standard Treatments for Health Centers was published.

The standard treatments for 100 conditions were included in the manual along with information on medicine interactions, growth curves, and other reference information. For each health problem, the manual included key diagnostic features and recommended treatments.

The treatments were published in a compact, but not quite pocket-sized, manual with a glossy green cover that bore the ministry logo. The manuals eventually were sent to all health centers. Since schools of medicine and other health education institutions fall generally outside the control of the Ministry of Health, little effort was made to have direct contact with these educational programs.

“However,” concluded Dr. Pedro, “since publishing the Standard Treatments for Health Centers, the CDD Program (Control of Diarrhea Disease), the ARI Program, and the TB (tuberculosis) program have all changed their treatment recommendations. Clearly what is needed to promote proper medicine use is to revise, reprint, and redistribute the Standard Treatments.”

Health Center Treatment Patterns—1997

Mrs. Soma, from Pharmaceuticals, had been quiet up to this point, but Dr. Pedro’s last comment troubled her. Politely, but firmly she began, “I’m not quite so sure that revising and redistributing the Standard Treatments is the answer.” She then went on to briefly review two surveys which she and her colleagues at Pharmaceuticals had recently carried out.

The first study, in which Mr. Joko’s staff had also been quite active, took last year’s medicine order and compared it to a rough estimate of what would have been needed if the disease pattern reported by the monitoring group at Preventive Health Services had been treated according to Dr. Pedro’s standards.

“Look here,” said Mrs. Soma, “your standard treatments would have the health center staff using large amounts of procaine penicillin, oral penicillin, and co-trimoxazole, while last year they ordered almost none of those antibiotics. Your treatments would have cut back on tetracycline, ampicillin, chloramphenicol, some of the injectables, and other popular medicines.”
medicine names meant nothing to Mr. Joko, but he understood that the standard treatments implied quite different consumption patterns than current practice.

Now in full stride, Mrs. Soma moved on to the second study, which her group had completed only last week. “The Standard Treatments manuals were sent out in 1996. We have just completed a survey of 2,500 patient cards from six randomly selected districts in East Kalija province.” In the treatment of common gastroenteritis (omitting cases of dysentery or suspected cholera), for which Dr. Pedro’s group recommended only rehydration, the average patient was getting more than three medicines. Virtually every patient was getting an antibiotic. More vitamins and minerals were being prescribed than oral rehydration salts. Antibiotics used for the under age five patients alone included oxytetracycline injection, tetracycline capsules, metronidazole, trisulfa, tetracycline syrup, ampicillin syrup, chloramphenicol suspension, and procaine penicillin injection. Some of the medicines recommended in the Standard Treatments are not available.

Similarly, for influenza and acute upper respiratory infections, Dr. Pedro’s group had recommended paracetamol for fever and aches, antihistamines for congestion, and a cough medicine. Yet, nearly every patient got an antibiotic, which was supplemented by an average of two other types of medicines. The range of different antibiotics prescribed was again quite impressive, at least a dozen by Mrs. Soma’s tally.

Mr. Joko was again mystified by most of Mrs. Soma’s medicine names, but he clearly sensed her feeling that the bright green Standard Treatments for Health Centers had not achieved its purpose. The twinkle in Dr. Pedro’s eye was beginning to fade.

**A Second Edition?**

Having shared the results of the directorate’s studies, Mrs. Soma somehow felt less compelled to support Dr. Pedro’s plan to simply revise, reprint, and redistribute the Standard Treatments. The meeting continued another 15 minutes. Mr. Joko raised some procedural questions, and Dr. Pedro asked the group’s opinion about the design and color of the cover.

Dr. Karma, always the diplomat, suggested that the project perhaps could support both Dr. Pedro’s revision of the Standard Treatments and another series of studies by Mrs. Soma’s group. He asked the group members to accompany him to the meeting with Mr. Domingo to propose how best the treatment guidelines could be revised and implemented.
Annex 2. Publications Relevant to the Development of STGs

The following publications are just some examples of standard treatment guidelines developed by countries and health care organizations. More recent editions may be available.

<table>
<thead>
<tr>
<th>Country</th>
<th>Title</th>
<th>Available from</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Analgesic Guidelines</em>, 3rd ed. (1997)</td>
<td>E-mail address: <a href="mailto:vmpf@vicnet.net.au">vmpf@vicnet.net.au</a></td>
</tr>
<tr>
<td></td>
<td><em>Gastrointestinal Drug Guidelines</em>, 1st ed. (1994)</td>
<td>Past editions of these guidelines may be available for the cost of postage.</td>
</tr>
<tr>
<td>Kenya</td>
<td><em>Clinical Guidelines for the Diagnosis and Treatment of Common Hospital Conditions in Kenya</em> (Nov. 1994)</td>
<td>Ministry of Health, Nairobi, Kenya</td>
</tr>
<tr>
<td>Malawi</td>
<td><em>Standard Treatment Guidelines</em> (available in both pocket and desktop versions) (1993)</td>
<td>Malawi Essential Drugs Programme, PO Box 30390, Lilongwe 3, Malawi</td>
</tr>
<tr>
<td></td>
<td><em>The Malawi Prescriber’s Companion</em> (1993)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fax: (977-1) 244927</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E-mail: <a href="mailto:dda@npl.healthnet.org">dda@npl.healthnet.org</a></td>
</tr>
<tr>
<td>Uganda</td>
<td><em>Uganda Essential Drugs Manual</em> (1997)</td>
<td>Ministry of Health, Uganda Essential Drugs, Management Programme, Central Medical Stores,</td>
</tr>
<tr>
<td>Country</td>
<td>Title</td>
<td>Available from</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>EDLIZ (Essential Drugs List for Zimbabwe) (1994)</td>
<td>PO Box 16, Entebbe, Uganda</td>
</tr>
<tr>
<td></td>
<td>A series of 15 modules on clinical and management topics is also available.</td>
<td>Zimbabwe Essential Drugs Action Programme, Ministry of Health, Box 8168, Causeway, Harare Zimbabwe</td>
</tr>
</tbody>
</table>
Drug and Therapeutics Committee
Training Course

Session 11.
Drug Use Evaluation
SESSION 11. DRUG USE EVALUATION

Purpose and Content

Session 11 provides information on the concept of drug use evaluation (DUE), a quality assurance method that is used worldwide, especially in North America and Europe, and that has been shown to be effective in identifying medicine use problems and as a method to improve medicine use. A broad-based, ongoing, systematic DUE program is valuable in promoting and improving rational use of medicines in hospitals and clinics.

Objectives

After attending this session, participants will be able to—

- Understand the concept of DUE
- Understand the process for implementing and performing a DUE
- Discuss the use of a DUE for improving pharmaceutical therapy
- Prepare criteria and thresholds for a DUE

Preparation and Materials

Read the following—

- Participants’ Guide

Key Definition

Drug use evaluation (DUE)—An ongoing, systematic, criteria-based program of medicine evaluations that will help ensure appropriate medicine use. If therapy is determined to be inappropriate, interventions with providers or patients will be necessary to optimize pharmaceutical therapy. This terminology is similar to that drug use review (DUR) and medication use review (MUR).

Introduction

The Drug and Therapeutics Committee (DTC) is responsible for many important pharmaceutical management activities; two of the most important ones are identifying medicine use problems
and implementing strategies to alleviate these problems. All DTCs should be actively involved in the evaluation and selection of new medicines for the formulary and the provision of these medicines to practitioners. It must also ensure that these medicines are being used correctly so that patients receive the maximum benefit from their pharmaceutical therapy.

Many strategies can be implemented to improve medicine use including educational programs, standard treatment guidelines (STGs) and other managerial activities, and regulatory programs. Session 11 provides participants with more in-depth information concerning the important managerial strategy of DUE. A DUE will—

- Define appropriate medicine use (by establishing approved criteria)
- Audit criteria against what is being prescribed
- Provide feedback to prescribers on all identified problems
- Monitor to see if criteria are followed and prescribing is improved

**The Need for DUE**

Irrational medicine use has occurred for as long as medicines have been available. In treating patients with modern medicines, several choices of therapy are available—rather than just one that all providers must follow. This increased number of medicines and treatment options serves to increase the number of irrational medicine treatment encounters and, ultimately, poor patient outcomes. Casual observation, as well as more systematic study of prescribing practices, frequently reveals a pattern of diversity among prescribers in the treatment of even the most common conditions.

Polypharmacy is one problem; providers may use three, four, five, and sometimes more medicines to treat the most trivial conditions for the sake of satisfying a patient’s need to receive medicines (or the pharmaceutical seller’s need for profit). Other reasons for polypharmacy include lack of diagnostic competence or confidence and an inadequate knowledge of treatment regimens. Other common medicine use problems are choosing incorrect medicines, prescribing the incorrect dose, prescribing medicines that cause adverse drug reactions (ADRs) or medicine interactions, and using more expensive medicines when less expensive medicines would be equally or more effective. Other medicine use problems that suggest a need for DUE include the following—

- Problems indicated from World Health Organization (WHO)/Management Sciences for Health (MSH) indicator studies
- High number of ADRs
- Signs of treatment failures
- Excessive number of nonformulary medications used
• Use of high-cost medicines where less expensive alternatives exist
• Excessive number of medicines within a therapeutic category

DUE, a system of improving the quality of medicine use in hospitals and clinics, is an ongoing, systematic, criteria-based program of medicine evaluations that will help ensure that appropriate medicine use is provided. A DUE can be structured so that it will assess the actual process of administering or dispensing a medicine (i.e., appropriate indications, dose, medicine interactions) or assess the outcomes (i.e., cured infections, decreased lipid levels.) Objectives of a DUE are as follows—

• Ensuring that the pharmaceutical therapy meets current standards of care
• Promoting optimal medication therapy
• Preventing medication-related problems
• Identifying specific medicine use problems that require further evaluation
• Creating guidelines (criteria) for appropriate medicine use
• Defining thresholds for quality of medicine use
• Enhancing accountability in the medicine use process
• Controlling pharmaceutical cost

A DUE system can be established in a short period once it has become clear what medicine use problems exist. Many of these problems can be identified from other DUE studies, a review of aggregate data in the hospital (e.g., most costly medicines, most prescribed medicines, ADR records), medical chart reviews, hospital and clinic medicine use indicators, or recommendations of DTC members. Regular meetings of the DTC and assessments of quality measurements in the health care system should be able to identify problems that can be addressed in a DUE for resolution.

A Stepwise Approach to DUEs

The following eight steps outline the basic information necessary to start and maintain a DUE program.

**Step 1. Establish Responsibility**

Responsibility falls to the DTC or a subcommittee of the DTC that functions only to monitor DUEs in the hospital or clinic. The DTC should undertake this responsibility with considerable interest, because this process can solve many medicine use problems, as has proven to be the case in many countries where this quality assurance function has been fully utilized.

The DTC or a subcommittee must establish procedures that will govern the committee in its activities concerning medicine use review and evaluation. As part of the responsibility of the DUE function, the DTC must establish a plan, outlining which medicines will be a part of the DUE process. This plan needs to be updated and evaluated each year.
Step 2. Develop Scope of Activities

The DTC should assess and identify medicine use problems and using this information to develop a scope of activity for the DUE program. The scope can be extensive or it can focus on a single aspect of pharmaceutical therapy. Methods to identify medicine use problems include and ABC or vital, essential, nonessential (VEN) analysis, defined daily dose analysis, ADR reports, medication error reports, antibiotic sensitivity results, procurement studies, hospital and primary care clinic indicator studies, patient complaints or feedback, and staff feedback. These screening mechanisms serve to provide the DTC with information concerning medicine use that would need further evaluation in a DUE.

Because of the large number of medicines available at a hospital or clinic, the DTC must concentrate on the most important medicines, those with the highest potential for problems, to get the most return on the work involved. These high priority areas would include—

- High-volume medicine use
- Medicines with a low therapeutic index
- Medicines with a high incidence of ADRs
- Expensive medicines
- Medicines that are critically important, including those in the following categories: cardiovascular, emergency, toxicology, oncology, intravenous medicines, and narcotic analgesics
- Antimicrobial medicines, both prophylactic and therapeutic
- Injections
- Medicines undergoing evaluation for addition to the formulary
- Medicines used for off-label indications
- Medicines used for high-risk patients

Steps 3 and 4. Establish Criteria, Define and Establish Thresholds

Criteria are statements that define correct medicine use. Establishing criteria is the single most important procedure in a DUE. Criteria for the use of any medicine should be established by the DTC using relevant evidence-based literature sources and recognized international and local experts. The criteria for any DUE should reflect what is in the country’s STGs (assuming that they have been developed correctly) and any medicine-use protocols that exist. Credibility of the DUE relies on criteria that are based on evidence-based medicine. Criteria must be developed with and accepted by the medical staff for the process to be credible.
Criteria should be developed for three to five of the most important indicators for each aspect of medicine use. Reviewing larger numbers of indicators will make for a more difficult DUE process and may significantly impair the outcomes of the review. This is not to say that more extensive use of indicators should not be reviewed, only that results are more easily obtained and possibly more meaningful when the scope is narrowed to include only the most important aspects of care.

After developing criteria, the DTC must establish a threshold or standard (benchmark) against which the criteria will be judged. A threshold refers to the percentage of charts or records that will meet or exceed the established criteria for the medicine. Ideally, this threshold will be 100 percent, but realistically, a smaller percentage will be more appropriate to account for exceptions to routine medicine prescribing. Therefore, a threshold of 90 to 95 percent is typically used for many criteria, but each instance must be carefully analyzed before reaching a conclusion.

A comprehensive list of indicators for appropriate medicine use includes the following components (see table 1 for an example of application)—

- **Process indicators**
  - Indications—specific uses for the medicine in question
  - Dose—specific doses for any approved indication for appropriate duration
  - Quantity dispensed—correct number of doses administered
  - Preparation—steps involved with preparing a medication for administration
  - Monitoring—laboratory test necessary and intervals of testing during the use of the medicine
  - Contraindications—known contraindications
  - Drug interactions—significant medicine interactions, including medicine-medicine, medicine-food, and medicine-laboratory
  - Administration—specific steps necessary to administer a medicine, especially for injectables
  - Patient education—instructions and education that a patient should receive with the medicine

- **Outcome indicators**—specific outcomes to be realized from medicine use
  - Lowered blood pressure, stabilized blood glucose, and fewer migraine and asthma attacks
  - Decreased visits to the emergency room, decreased hospitalizations
- Improved patient quality of life (obtained from questionnaires)
- Pharmacy administration indicators
  - Correct cost to patient
  - Accurate billing records
  - Accurate dispensing records
  - Appropriate use of generic medicines or therapeutic equivalents
  - Appropriate use of formulary medicines
  - Appropriate quantity dispensed

### Table 1. Sample DUE Criteria for Ciprofloxacin

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Criteria</th>
<th>Threshold, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Complicated, chronic, or relapsing urinary tract infection (UTI)</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Gonorrhea Way resistant respiratory tract infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostatitis Prostatitis Gastrointestinal (GI) infections</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Complicated or recurrent infections: 500–750 mg bid</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>GI infections: 500 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gonorrhea: 250 mg in 1 dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose in renal disease decrease as follows:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance (CrCl) 30–50 ml/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– 250–500 q 12 h 5–29 ml/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– 250–500 q 18 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemodialysis—500 mg q 24 h</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Complicated UTI: 10–21 days</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Respiratory: 7–14 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis: 4–6 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GI infection: 5 days</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnancy  Children younger than 18</td>
<td>100</td>
</tr>
<tr>
<td>Medicine interactions</td>
<td>Medicines—theophylline, antacids, iron, sucralfate, probenecid</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Food: decreased absorption with milk</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Negative cultures</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Improved symptomatology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No treatment failures</td>
<td></td>
</tr>
</tbody>
</table>
Step 5. Collect Data and Organize Results.

DUEs can be accomplished as prospective evaluations, or they can be performed retrospectively. A prospective analysis involves the collection of data as the medicine is being prepared or dispensed to the patient. Retrospective analysis is done using chart reviews or other data sources to review medicine use according to indicators and criteria prepared in advance. The advantage of a prospective review is that the pharmacist (or other reviewer) can intervene at the time the medicine is dispensed to prevent errors in, for example, dosage, indications, or interactions. Retrospective evaluation, which may involve more of the reviewer’s time or require access to medical records, is best accomplished when the reviewer has time away from the patient care areas and distractions. Typically, medicine-related criteria that are reviewed in these types of evaluations are as follows—

- Prospective studies (obtained from prescription records)
  - Indication
  - Dose
  - Duration of therapy
  - Dosage form and route of administration
  - Potential medicine interactions
  - Appropriate therapy and medicine selection (corresponds to STGs)
  - Therapeutic duplication
  - Contraindications
  - Quantity dispensed

- Retrospective studies (obtained from prescription, medical records, laboratory records)
  - Laboratory monitoring
  - Monitoring therapeutic use of high-cost medicines
  - ADRs to medications
  - Correct use of generic or therapeutic equivalents
  - Patient outcomes from pharmaceutical therapy

Collection of the data is performed by reviewing a suitable sample of charts or prescription records from the health care facility, usually by selected pharmacy personnel. At a minimum, 50 to 75 records should be reviewed at each health care facility. The larger the facility and the more practitioners who are available, the larger the percentage of records that would need to be reviewed and analyzed.

An illustrative sample of a collection form, indicators, criteria, and thresholds can be found in annex 1.

In some countries, computerized systems automatically address the criteria in the process of entering patient information into the computer. Pharmacists then must evaluate any indicators that do not meet established criteria (i.e., dose, medicine interactions, duplicate medicines in the same therapeutic class, and others that may appear in the patient records in the computer program). These problems then must be corrected before the medicine is dispensed. This system
is also useful because of the large number of patients that can actually be evaluated and the subsequent database that would be produced.

**Step 6. Analyze Data**

Data are collected, tabulated, and analyzed to see if criteria and thresholds are met. The following important steps should be completed when analyzing data—

- Tabulate results for each indicator
- Analyze results to see if the criteria are met and the thresholds are not exceeded
- Determine why thresholds are not met
- Analyze data quarterly or more frequently

If a threshold is not met, it may indicate a medicine use problem that requires the attention of the DTC.

**Step 7. Develop Recommendations and Action Plan**

After completing the data analysis, information is presented to the DTC and a decision is made as to the appropriateness of the information in the DUE. The DTC also must decide on whether to continue, discontinue, or expand the functions of the DUE in question. All medicines that do not meet the thresholds must be evaluated carefully and plans must be made to improve the use of the medicine relative to the criteria.

Recommendations should be prepared for the DTC to address the following—

- Inappropriate medicine use
- Unacceptable patient outcomes
- Methods to resolve any medicine use problem

Recommendations should include specific steps to correct any medicine use problem that is evident from performing the DUE. For example, if a specific medicine is being prescribed at a high dose, then the recommendations need to reflect this and how the DTC might improve the dosing of this medicine. Interventions to improve medicine use might include—

- Education, including letters to practitioners, in-service education, workshops, newsletters, and face-to-face discussions
- Implementation of medicine order forms
- Prescribing restrictions
- Formulary manual changes
- Change (or better enforcement) of the STGs
Step 8. Conduct DUE Follow-up

Follow-up in every DUE is critical to ensure resolution of any unresolved medicine use problems. The DUE may have identified new problems that need to be resolved within the health care system. If the problems are not resolved, then the DUE will have little usefulness to the health care system. As a part of a follow-up plan, the DTC must assess the need to continue, modify, or stop the DUE activity depending on the results of each specific medicine review.

A DUE should be an ongoing process in which medicine-related problems are regularly addressed. Medicine review should be considered a long-term program, one that is continuously updated and revised to reflect current situations and needs within the health care institution.

All programs within the DTC should be evaluated yearly. This complete evaluation is necessary to look comprehensively at the entire program and analyze its merits and its utility in improving medicine use. Programs that do not have a significant impact on medicine use should be redesigned so that they can provide measurable improvements. Without improvements in medicine use and patient outcomes, the time spent on DUE will be of no value.

It must be stressed that indicators and criteria for a DUE can be highly individualized depending on the specific needs of the health care facility.

When DUEs Go Wrong

Some problems in the DUE procedure will serve to make this process ineffective. Because it is a complicated, multifactorial process, it may easily get bogged down and become an ineffective evaluation. Some of the difficulties and their solutions are—

- Lack of authority and organization—The DUE must have a clear organizational structure defined including, for example, what person develops criteria, collects data, and reports results. Clinicians must be involved in the development.

- Poor problem prioritization—Poor prioritization may lead to work on medicine use problems that may be insignificant and make meaningful results difficult to obtain.

- Poor documentation—All activities should be documented with a report in the DTC minutes, and this report should be distributed to the medical staff as necessary; documentation should clearly discuss results and recommendations of each DUE.

- Inadequate follow-up—This problem is one of the most frequent to occur with DUE; follow-up and resolution of every problem must be accomplished with every DUE.
• Overly intrusive data collection and evaluation—This process can consume many individuals’ time and must be kept to a minimum to accomplish the task of the DUE; DUEs in general must not take a significant amount of time away from patient care.

• Failure to obtain “buy in” from medical staff

The performance of a DUE must be kept in perspective at all times. If a DUE becomes very time-consuming with only minimal results, then the methodology must be changed and the DUE restructured (in terms of criteria, data collection, and interventions) to provide meaningful results. The objectives of all DUEs are to identify and correct medicine use problems and consequently improve patient outcomes. A DUE should never become just an exercise in collecting and disseminating information.
Activity 1. Developing a DUE

For activity 1, assume that your DTC has information derived from indicator studies, chart reviews, and ABC analysis that shows that many antimicrobial medicines are being used inappropriately (see Activity 1. Developing a Guideline for Use during the Field Trip in session 10, “Standard Treatment Guidelines”). There are anecdotal reports of inappropriate use (e.g., wrong dose, wrong combination of medicines, lack of baseline laboratory studies) for several antimicrobial medicines.

The DTC has revised the STGs for treating pneumonia and for surgical prophylaxis. The DTC has also provided extensive education to physicians and nurses concerning appropriate treatment including face-to-face education and in-service education programs. Because this problem is significant, the DTC recommends that a DUE be implemented to assess and confirm that the educational activities and revised STGs have effectively changed prescribing habits.

Each group should develop DUE criteria and thresholds for the antimicrobials that are a part of the STG for pneumonia or caesarian section prophylaxis.

Summary

DUE is an audit and feedback intervention in which medicine use can be reviewed against approved criteria. A DUE requires the establishment of criteria and thresholds and the review of medicine use to determine if therapy is appropriate. Feedback to prescribers is necessary to improve prescribing and educational, managerial, and regulatory interventions may be required to improve the use of medicines.

A DUE will help improve medicine use by—

- Ensuring that the pharmaceutical therapy meets current standards of care
- Promoting optimal medication therapy
- Preventing medication-related problems
- Identifying specific medicine use problems that require further evaluation
- Creating guidelines (criteria) for appropriate medicine use
- Define thresholds for quality of medicine use
- Enhancing accountability in the medicine use process
- Controlling medicine cost

DUE methodology has been successful in many parts of the world. By using appropriate planning, development, and follow-up and by implementing appropriate interventions when problems are discovered, improved patient outcomes will be the result.
Annex 1. Example of Established DUE Criteria on Data Collection Form for Amikacin

<table>
<thead>
<tr>
<th>Date:</th>
<th>Medicine: AMIKACIN</th>
<th>Data collector’s initials: ___________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Chart No.</th>
<th>Diagnosis</th>
<th>Age/Sex/Weight</th>
<th>Date Treated</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Criteria and Indicators</th>
<th>Threshold</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Justification for medicine being prescribed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Serious infections caused by susceptible strains of aerobic gram-negative bacteria resistant to gentamicin and tobramycin</td>
<td>95%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
<tr>
<td>2. Suspected serious gram-negative infections acquired in the hospital with high resistance rates to gentamicin and tobramycin</td>
<td>95%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
<tr>
<td>3. In combination with an antipseudomonal penicillin when treating serious pseudomonas infections</td>
<td>95%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Process criteria</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Obtain serum creatinine before therapy or within 24 hours of initiation of therapy</td>
<td>100%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
<tr>
<td>5. Loading dose of 7.5 mg/kg (IV or IM) based on ideal body weight</td>
<td>100%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
<tr>
<td>6. Maintenance dosage range of 15 mg/kg/day ideal weight (exception: renal compromise)</td>
<td>100%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
<tr>
<td>7. Therapy changed to tobramycin, gentamicin, or other medicine if culture and sensitivity indicate less expensive or more appropriate medicine</td>
<td>100%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome criteria</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Clinical improvement noted in patient medical records</td>
<td>90%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
<tr>
<td>9. Fever reduction to normal within 72 hours</td>
<td>90%</td>
<td>Yes No Yes No Yes No Yes No Yes No</td>
</tr>
</tbody>
</table>
Drug and Therapeutics Committee
Training Course

Session 12.
Infection Control
SESSION 12. INFECTION CONTROL

Purpose and Content

Session 12 introduces basic infection control (IC) practices for members of Drug and Therapeutics Committees (DTCs). An IC program, working in conjunction with an active DTC, is an essential tool in hospitals for preventing and controlling nosocomial infections and the morbidity, mortality, and cost associated with them.

As with many of the sessions in this DTC training course, participants are encouraged to review the articles in the “Further Readings” section for more information. Session 12 is brief, providing basic information primarily for DTC members, and cannot provide all the information and skills necessary for implementing a comprehensive IC program.

Objectives

After attending this session, participants will be able to—

- Understand basic infection control concepts
- Understand the causes of nosocomial infections
- Understand the components of an infection control program
- Understand how the Infection Control Committee and the DTC can decrease the incidence of nosocomial infections and antimicrobial resistance (AMR)

Outline

- Key Definitions
- Activity 1
- Introduction
- Epidemiology of Nosocomial Infections
- Control and Prevention of Nosocomial Infections
- Core Strategies for Reducing the Risk of Nosocomial Infections
- Implications for the DTC
- Activity 2
- Summary

Preparation and Materials

Read the Participants’ Guide.
Key Readings


Websites for infection control information, guidelines, training materials, and articles are available from the U.S. Centers for Disease Control and Prevention, the World Health Organization, EngenderHealth, and American International Health Alliance (see annex 1 for website addresses).

Key Definitions

**Infection control**—The process by which health care facilities develop and implement specific policies and procedures to prevent the spread of infections among health care staff and patients.

**Nosocomial infections**—Infections contracted by a patient or staff member while in a hospital or health care facility (and not present or incubating on admission)

**Disinfection**—A process of microbial inactivation that eliminates virtually all recognized pathogenic microorganisms, but not necessarily all microbial forms (e.g., spores)

**Sterilization**—The use of physical or chemical procedure to destroy all microbial life, including large numbers of highly resistant bacterial endospores. Procedures include steam, heat, and chemical sterilization.
Activity 1. Describing Infection Control Practices at Your Facilities or Institutions

Describe your hospital IC program or current practices at your hospital or clinic (or at the ministry level). Include the following—

- Committee membership
- Written or updated policies and procedures
- Surveillance of nosocomial infections
- Hand hygiene and use of gloves
- Isolation and universal precautions
- Cleaning strategies (housekeeping), including waste disposal
- Cleaning, disinfection, and sterilization of instruments and supplies
- Intravenous (IV) catheter and IV fluids and medication
- Urinary catheters and urine drainage systems
- Mechanical ventilation and respiratory equipment
- Surgical site care
- Food and water monitoring
- Training
- Employee health and immunization for staff
- Antimicrobial use monitoring

As a part of this exercise, please answer the following questions concerning your IC program or practices—

- Are you satisfied with the infection control procedures and activities?
- Is infection control maintained throughout your health care system?
- Are there complaints of inadequate infection control and resultant nosocomial infections that infect patients or health care staff?
- Is there a formal mechanism for reporting and investigating nosocomial infections?
- Are outbreaks of infectious diseases in the hospital a common problem? What is the usual source of the outbreak?
- Is the DTC involved in any infection control activities? Please describe these activities.

In your groups, discuss each individual IC program, select one, and be prepared to present a summary of the program.
Introduction

The spread of infectious diseases in hospitals between patients and staff is a serious problem worldwide. These hospital-acquired infections (called *nosocomial infections*) contribute to morbidity and mortality in hospitals and health care facilities and increase costs significantly. Using a conservative nosocomial infection rate of 15 percent for developing countries (based on rates in South Africa) and a 5 percent mortality rate, it can be concluded that hospital-acquired infections rank as one of the most important causes of death in the developing world.\(^{19}\) The liberal and inappropriate use of antimicrobial agents in health care facilities has resulted in the emergence of AMR bacteria. Ineffective IC practices at hospitals have also facilitated the spread of these resistant bacteria. The overuse of wide-spectrum antimicrobials further contributes to the problem.

The goal of IC programs is to decrease and minimize the spread of infections between patients and providers in health care facilities. Evidence is clear that IC programs are effective in decreasing the rates of infection, morbidity, and mortality, as well as in decreasing costs associated with infections. The magnitude of the nosocomial infection problem is significant, because many hospitals will have infection rates that exceed 10 percent, although most of these infections are preventable.

Who is responsible for infection control? Ideally, an Infection Control Committee (ICC)—but the entire health care community is responsible for developing and following procedures to prevent infections. Because it can play a pivotal role in assisting the ICC and in leading the hospital in IC activities, the DTC bears much of the responsibility. Some authorities believe that effective ICCs and DTCs will provide the basis for developing more comprehensive quality assurance programs throughout the health care organization.

Epidemiology of Nosocomial Infections

Simply stated, patients and health care staff can spread infectious diseases directly to each other, and then these diseases can be transmitted to family and community members. These infections are more prevalent in hospitals, where health care staff and patients are at risk. Primary health care clinics also have significant problems with nosocomial infections, although not to the extent found at the larger, overcrowded hospital centers.

Hospital personnel most at risk for contracting and spreading infections include those involved with (a) invasive procedures; (b) direct exposure to patients during examinations; (c) exposure to blood, sputum, and other body fluids; and (d) exposure to environmental pathogens (air, food, water, or inanimate objects). Physicians and nurses are most at risk, but housekeeping personnel, who come in contact with infectious waste, needles, and other sharps and with contaminated disinfectants and supplies, also face a high risk.

The most likely sites for nosocomial infections include surgical incisions, the urinary tract, the lower respiratory tract, and the bloodstream. Skin and soft tissue infections and gastrointestinal infections are also common.\textsuperscript{20}

**Common Antimicrobial Resistant Bacteria**

Nosocomial infections continue to increase in the developed world with most infections being caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus and gram negative-bacteria (*Escherichia coli*, *P. aeruginosa*, *Enterobacter* spp., and *Klebsiella pneumoniae*). These gram negative-bacteria are resistant to penicillin derivatives through the production of beta-lactamases, but also are becoming resistant to aminoglycosides and carbapenems. These resistant pathogens are also increasingly documented in developing countries.\textsuperscript{21} Infections with MRSA are common and resistance to methicillin continues to grow. Forty to sixty percent of all *S. aureus* acquired in the hospital are methicillin-resistant and typically multidrug resistant. The disease is a common complication of wounds, lower respiratory tract infections, septicemia, invasive devices, pressure sores, burns, and ulcers.\textsuperscript{22}

In recent years, nosocomial transmission of community-acquired, multidrug-resistant organisms including *pneumococcus*, *Mycobacterium tuberculosis*, *salmonella* spp, *shigella* spp, and *V. cholerae* has been documented in developing countries.\textsuperscript{23} Extensively drug-resistant (XDR) tuberculosis has spread among hospitalized patients in South Africa. According to a recent study, about 1,300 cases of XDR tuberculosis are predicted to occur in a single region of South Africa by the end of 2012 (if no new interventions are introduced), more than half of which are likely to be nosocomially transmitted.\textsuperscript{24} The prevalence of active TB and the presence of susceptible HIV-infected patients in the hospital, combined with inadequate IC practices and procedures, increase the likelihood that *M. tuberculosis* will be transmitted in hospital settings.

The spread of bloodborne viruses and bacteria also represent significant threats to health care staff and patients. HIV, as well as hepatitis B and C, can be transmitted through needle sticks and blood transfusions. Transmissible pathogens may also put patients and staff at risk for fungal infections (candida), protozoal infections, scabies, giardiasis, amebiasis, and some vector-borne diseases.

**Root Causes**

Root causes of nosocomial infections and AMR problems in hospitals include the following—

- Lack of training in basic IC

\textsuperscript{20} http://www.cdc.gov/ncidod/dhqp/hai.html; 2008
\textsuperscript{24} Basu et al, *Lancet* 2007;370:1500-07
• Lack of an IC infrastructure and poor IC practices (procedures)

• Inadequate facilities and techniques for hand hygiene

• Lack of isolation precautions and procedures. Large medical and surgical wards promote the transfer of infections to other patients and health care personnel

• Use of advanced, complex treatments without adequate supporting training and infrastructure, including—
  o Invasive devices and procedures
  o Complex surgical procedures
  o Interventional obstetric procedures
  o Intravenous catheters, fluids, and medications
  o Intravenous catheters
  o Urinary catheters
  o Mechanical ventilators

• Inadequate sterilization, disinfection, and hospital cleaning procedures and practices

Control and Prevention of Nosocomial Infections—Infection Control Committees

The ICC oversees the control and prevention of nosocomial infections in hospitals and clinics. This committee acts much like a DTC and cooperates with a DTC to control these infections. An ICC typically will have a physician, nurse, laboratory microbiologist or technologist, and other members, all of whom review surveillance data and institute policy and procedures. Other members may include hospital administration, medical staff (such as an infectious disease specialist, surgeon, or an obstetrician/gynecologist), laboratory, central sterile supply, housekeeping, and pharmacy staff. The ICC membership may be similar to that of the DTC, and the two committees may, in fact, share some of the same members. All individuals on the committee must have the formal training to effectively carry out the committee’s functions.

To be effective and productive, the committee must also have the necessary authority and scope of activity. A direct line of authority from the hospital administration and Ministry of Health officials is required. The committee authority of should include the right to examine patients, take cultures if necessary, isolate patients, and close wards in outbreaks. The recommendations and actions of the committee should be disseminated throughout the hospital and enforced.

The goal of the ICC is to prevent the spread of infections within the health care facility. Primary functions include the following—

• Addressing food handling, laundry handling, cleaning procedures, visitation policies, and direct patient care practices, including hand washing and immunizations.

• Obtaining and managing critical bacteriological data and information, including surveillance data
• Developing and recommending policies and procedures pertaining to IC
• Recognizing and investigating outbreaks of infections in the hospital and community
• Intervening directly to prevent infections
• Educating and training health care workers, patients, and nonmedical caregivers

An important part of an ICC or program is the establishment of policies and procedures. These procedures must be comprehensive and written to ensure stepwise control of all issues involving IC. As with the DTC, policies and procedures provide the infrastructure for developing a comprehensive program that is both effective and enforceable. At a minimum, policies and procedures should be in place for hand hygiene and the use of gloves, isolation and universal precautions, insertion of invasive devices, use of urinary catheters, housekeeping, disinfection and sterilization, mechanical ventilators and respiratory equipment, and surgical site care. Policies should focus on (a) making clinical staff aware of all required procedures to control and prevent infections, and (b) monitoring compliance with policies and procedures.

Surveillance activities are an important part of IC, but they must be prioritized. The collection of information that is infrequently evaluated or of little importance should be discouraged in favor of concentration on priority areas. Surveillance should include the following—

• Daily visits to medical wards by the IC nurse (especially high-risk wards such as intensive care units and surgical wards) to observe for infection, and record keeping to document the results of these visits
• Review of results of the microbiological laboratory, including sensitivity patterns to antibiotics (if available) and reporting these findings to appropriate medical staff
• Attention to spontaneous reports from different wards concerning possible occurrence of nosocomial infections.

ICCs also oversee a number of important functions in their effort to control nosocomial infections. These functions are discussed in the following sections.
Core Strategies for Reducing the Risk of Nosocomial Infections

**Hand Hygiene and the Use of Gloves**

Hand hygiene is considered to be the most important procedure for preventing nosocomial infections. With the appropriate facilities and supplies, this simple method of infection control will decrease nosocomial infections significantly. Sinks with running clean water and soap are typically necessary, but not essential. Where they are unavailable, waterless hand antiseptics can be used, with comparable results. Commercial preparations are available or can be manufactured locally by using isopropyl alcohol 70 percent with glycerin.

The use of disposable towels or single-use washable towels is encouraged in all hospitals. Reusable cloth towels are a source of contamination, and procedures must regulate how they will be used and laundered.

Absolute indications for hand hygiene are generally not known because of a lack of well-controlled studies. Touching or significant contact with possibly infected materials (e.g., blood, sputum, wounds, skin) necessitates thorough hand hygiene before after each contact.

**Specific Recommendations for Hand Hygiene**

Hand washing is recommended—

- Before performing invasive procedures
- Before taking care of susceptible patients (e.g., immunocompromised patients, newborns)
- Before and after touching wounds
- After situations during which microbial contamination may occur (e.g., contact with blood, mucus, feces, urine, sputum)
- After touching inanimate sources that may have contaminants
- Before and after contact with patients

Generally, superficial contact with sources not known to contain pathogens does not necessitate any hand hygiene.

**Hand Hygiene Technique**

Vigorous rubbing together of all surfaces of lathered hands for at least 20 seconds, followed by a thorough rinse using clean, uncontaminated water. Antiseptic-containing products should be used before caring for high-risk patients (such as newborns or immunocompromised patients) and before surgical procedures.
**Specific Recommendations for the Use of Gloves**

Use of gloves is encouraged for all surgical procedures and for patient examinations where contamination may be a risk. There are two important reasons for using gloves—

- To provide a protective barrier to prevent gross contamination from blood, body fluids, secretions, and wounds
- To prevent the transmission of pathogens from hands to patients

Wearing gloves does not eliminate the need for hand hygiene, because the gloves may have small defects or become torn during use. Failure to change gloves between patient contacts is an IC hazard.

Policies and procedures describing proper hand hygiene and the use of gloves should be established and made available to hospital staff. A system to monitor compliance with these policies is necessary. Observation checklists are useful to determine if hospital staff are applying appropriate hand hygiene practices.

**Isolation and Standard Precautions**

Patient overcrowding in hospital wards commonly leads to the spread of infectious diseases between patients and to hospital staff. This spread can be remedied by following procedures to isolate and protect individuals with communicable diseases.

Isolation and the use of standard precautions are necessary when patients present with communicable diseases such as acute respiratory infection, diarrhea, active tuberculosis, measles, chicken pox, and other common communicable diseases. Ideally, each of these patients should be placed in a single room, with appropriate isolation procedures. If a private room is not available, placement with other patients with the same infectious disease is necessary, along with appropriate barrier protection.

Standard precautions and isolation techniques include—

- Comprehensive written policies and procedures
- Patient placement and transport—private rooms when possible to limit the transmission of microorganisms to staff, visitors and other patients; use cohort rooming when patients are infected with the same pathogen.
- Visitation policy
- Hand hygiene and use of gloves as discussed above
- Masks, eye protection, face shields—for patient care activities that may generate splashes or sprays of blood or body fluids and for use of aerosolized contaminants
• Gowns and protective apparel—for significant splashes or exposure to bloodborne pathogens

• Sharp instruments and needles must be handled with care. DO NOT remove, bend, break, or manipulate needles from syringes by hand. Used needles, scalpel blades, and other sharps should be placed in puncture-resistant containers.

• Cleaning—rooms, cubicles, and bedside equipment should be cleaned appropriately as discussed in the next section

Cleaning Strategies (Housekeeping)

Adequate cleaning of the hospital on a regular schedule is one of the most important aspects of an IC program. The hospital’s cleanliness is the first thing a patient sees when entering the doors. A clean hospital not only is less likely to cause the spread of infectious diseases, but also creates a positive image and inspires confidence in its professional staff. The following recommendations will greatly reduce the risk of nosocomial infection related to sanitary conditions—

• Written policies and procedures that explicitly describe tasks and how they are to be done must be developed for the housekeeping staff.

• Cleaning should include a regular schedule of mopping floors with appropriate disinfectants. Toilets must be cleaned on a regular basis, because they may be a source of contamination within the hospital. Cleaning equipment must also be cleaned after each use to minimize the spread of potentially dangerous microorganisms. Cleaning walls and ceilings is not recommended unless they have become visibly soiled. The use of fogging disinfectants is not recommended.

• Waste disposal should include the burning of contaminated supplies, including needles, syringes, blood-contaminated materials, and so forth. Infective waste should either be incinerated or autoclaved before disposal in a local sanitary landfill.

• Disposable syringes with needles, scalpel blades, and other sharp items capable of causing injuries should be stored in a puncture-resistant container until disposition of the container. To prevent accidental needle stick and possible infection with a serious pathogen, do not to recap, bend, or cut needles, because these actions may cause an accidental puncture.

• Soiled linen should be bagged and isolated from the normal hospital traffic. Cleaning procedures should include washing in hot water (at least 71 °C/160 °F). Clean linen should be transported and stored, so that cross-contamination does not occur.
**Cleaning, Disinfecting and Sterilizing Instruments and Supplies**

The following recommendations will help to greatly reduce the risk of nosocomial infection related to nonsterile supplies—

- Written policies and procedures are necessary.
- All objects to be disinfected or sterilized should first be thoroughly cleaned to remove all organic matter.
- When sterilization is required, a steam sterilizer should be used unless the items being sterilized will be damaged by heat, pressure, or moisture. Sterilizers require appropriate loading and placement of items.
- Quality control in reprocessing is critical and requires specific policies and procedures that are closely followed at all times.
  - Monitor and record sterilization parameters (i.e., time, temperature, and pressure)
  - Chemical indicators should be used to ensure sterilization.
  - Biological indicators for steam sterilization should be used at least weekly.
- Sterilized items must be stored in areas that prevent the contamination of sterilized products.
- Items or devices manufactured for a single use should not be reprocessed.

**Careful Use of Intravascular Catheters, Intravenous Fluids, and Medications**

Invasive IV devices and medications can be lifesaving when used appropriately. When used inappropriately, they may result in life-threatening nosocomial infections. To maximize prevention of these infections, hospitals should have the following practices and policies—

- Comprehensive policies and procedures that address catheter placement, maintenance of catheters, and preparation of IV fluids and medications. Education programs to train and monitor personnel in this area are necessary.
- IV catheters and especially central venous catheters should be used only when absolutely necessary, because these devices are associated with a high rate of infection, especially when inserted with a cut-down procedure.
- The use of high-quality silicon elastomer or polyurethane catheters is recommended, because they are known to cause fewer infections. Avoid polyvinyl chloride materials, because they are known to increase infection rates.
- Manufacture of IV solutions requires strict Good Manufacturing Practices standards, and these solutions must be purchased from reliable suppliers that are known to have good
quality control. Contamination from improperly prepared solutions may be a significant cause of nosocomial infections.

- Medication admixtures to IV solutions should be prepared centrally by qualified pharmacy personnel. If this is not possible, specific policies and procedures should be prepared for nurses who should be certified competent before they are allowed to prepare admixtures. Use all lipid and parenteral nutrition solutions promptly.

**Proper Use of Urinary Catheters and Urine Drainage Systems**

Indwelling urinary catheters should be used only when absolutely necessary to relieve an obstruction of urinary flow or to monitor urine output in critically ill patients. They should be discontinued as soon as possible to decrease the risk of nosocomial infections. These devices are responsible for a high percentage of hospital infections. The following recommendations should be followed—

- Written policies and procedures are required for techniques of insertion, use, and maintenance of catheters.

- Only closed drainage systems should be used. Triple-lumen irrigation catheters should be available for patients undergoing urological surgeries for which frequent irrigation is necessary. Breaks in the system of any kind should be discouraged including for irrigation and obtaining urine samples.

- For selected patients, a condom drainage catheter, suprapubic catheterization, and intermittent urethral catheterization can be useful alternatives.

**Proper Use of Mechanical Ventilation and Respiratory Equipment**

The use of mechanical ventilation should be used only when absolutely necessary, because these devices can cause high rates of nosocomial infections. Specific policies and procedures are required if these devices are available in the hospital. Suctioning is important, and catheters should be used only once (or reprocessed appropriately). Suction contents should be disposed of properly and soon after collection. All equipment should undergo ethylene oxide sterilization or high-level disinfection before reuse. Other important guidelines include the following—

- Wean from mechanical ventilation as early as possible.

- Use heated humidifiers.

- Ensure proper handling of inhalation medications, nebulizers, and tubing.
Attention to Surgery and Surgical Site Care

The following interventions can help reduce the incidence of nosocomial infections related to surgery and surgical site care—

- Implement comprehensive policies and procedures.
- Minimize preoperative stays in the hospital.
- Avoid shaving patients unless absolutely necessary. In these cases, use hair clippers (or disposable razors when clippers are not available). Clipper heads must be disinfected between uses. If shaving is necessary, shave immediately before surgery and not the night before.
- Use antibiotic prophylaxis only when indicated. The appropriate medicine, dose, and interval must be used following established protocols. Usual prophylaxis involves a single dose of an antimicrobial 1–2 hours before procedure. Prescribing practices in this setting must be monitored to ensure correct use. Inappropriate use will contribute to AMR, adverse drug reactions, prolonged hospitalizations, and significantly higher costs.
- Ensure that dressing carts for surgical site cleaning and dressings do not contain instruments that are submerged between uses, because this practice may cause contamination of disinfectants. Sterile instruments should be provided in individually wrapped sterile packages.
- Use only effective antiseptics and disinfectants. Older disinfectants, such as benzalkonium chloride, should not be kept in stock, because of efficacy problems. As with selecting medicines for a formulary, antiseptics and disinfectants must be selected using an evidenced-based approach.
- Ensure that hand and forearm antisepsis for surgical team members includes perioperative scrub with an appropriate antiseptic scrub.

Education of Hospital Personnel

Educational programs that emphasize appropriate IC techniques and procedures are necessary for controlling nosocomial infections. Educational activities should focus on basic IC functions, including hand hygiene, housekeeping, aseptic technique, procedures for the preparation of IV fluids and medicines, care of ventilated patients, care of patients with indwelling urinary catheters, wound care and use of antiseptic solutions, isolation and universal precautions, effective use of microbiology laboratory services, and appropriate use of antimicrobials.
**Attention to Employee Health**

Employee health programs are necessary to monitor the health of all employees within the medical institution and to administer immunizations. The objectives of an employee health program include the following—

- Educating health care staff concerning IC
- Monitoring and investigating potentially harmful infections in employees
- Providing care to employees with work-related illness
- Providing immunizations to staff

As a part of any employee health program, the following vaccinations should be administered to decrease risk of contacting infections and transmitting infections to patients—

- Hepatitis A and B
- Influenza (yearly)
- Measles
- Rubella
- Varicella zoster
- Bacillus Calmette-Guérin (BCG)
- Polio vaccine
- Tetanus/diphtheria

**Proper Handling of Food and Water**

Food- and water-borne outbreaks in U.S. hospitals have been shown to be caused by contaminated food and water, inadequate cooking, infected food handlers, and contaminated equipment.

Written policies and procedures that describe proper food and water handling within the hospital environment are necessary to reduce the incidence of nosocomial infections.

**Careful Antimicrobial Use Monitoring and Evaluation**

This program is crucial in controlling the use of antimicrobials in the hospital. Control and restrictions on antimicrobials are essential to ensuring that antimicrobial treatment and prophylaxis are appropriate. Unnecessary and inappropriate use of antimicrobials results in prolonged hospital stays, adverse drug reactions, increased incidence of AMR, and increased costs.

The DTC and ICC should establish antimicrobial therapeutic guidelines, prophylactic guidelines, and specific guidelines for surgical prophylaxis. A monitoring system is essential to ensure appropriate use of these medicines.

The following case study (Donald Goldman, unpublished) illustrates inappropriate antimicrobial use in cesarean section surgical prophylaxis. This kind of antimicrobial use leads to increased infections, antimicrobial resistance, higher health care costs, and increased adverse drug reactions.

The risk of endometritis after cesarean section exceeds 30 percent and antimicrobial prophylaxis reduces the incidence by 66 percent. Two hospitals are compared for antimicrobial use in surgical prophylaxis of cesarean section procedures. Hospital A treats 70 percent of their patients with prophylaxis and 31 percent of patients receive prophylaxis within one hour after delivery. Hospital B treats 32 percent of their patients with prophylaxis and 70 percent of patients receive antimicrobials within one hour after delivery.

How would you describe the use of antimicrobial prophylaxis for these two hospitals?

- Hospital A uses a prophylaxis for too many patients because it should be used only for high-risk procedures. Only 32 percent received the medicine on time, adding to the inappropriate use in this case.

- Hospital B uses prophylaxis more appropriately (i.e., administered to the high-risk population) and gives the medicine at the appropriate time in 70 percent of cases—still too low for administering a single dose. This 70 percent represents an improvement over hospital A, but is still unacceptable because many failures will result from the poor timing of the doses. As antimicrobial administration is given closer to the surgical procedure, there is a corresponding decrease in the incidence of post-operative infections.

Appropriate antimicrobial prophylaxis is one of the most important activities that an IC program can do to reduce the incidence of nosocomial infection in cesarean section procedures. Administering these antimicrobials is within the capacity of staff to improve practices in almost all settings and results can be seen in a relatively short period of time.

Appropriate use of antimicrobials is an important issue for the DTC and the ICC. The committees must work together to achieve rational use.

**Implications for the DTC**

DTCs have the potential to manage formularies, improve the selection of medicines, identify medicine use problems, and implement strategies to improve the use of medicines. IC committees and programs assist in the control of infectious diseases and nosocomial infections within hospitals and primary care clinics. These two organizations can work together to significantly improve health care outcomes by controlling infectious diseases and ensuring appropriate medicine use at all levels. The synergy between the two committees can be dramatic in overall health care benefits, including significant cost savings.
Where a DTC and an ICC exist side by side, the DTC can be expected to provide the following—

- Support of all IC activities
- Training for ICC members on appropriate antimicrobial use
- Selection of appropriate antimicrobials, disinfectants, and antiseptics
- Selection of all antimicrobials to be used in the hospital, in relation to evidenced-based information
- Development and implementation of appropriate antimicrobial treatment guidelines, including surgical prophylaxis guidelines
- Monitoring of IV and injection preparation and administration
- Antimicrobial utilization reviews (i.e., DUE) and monitoring
- In cooperation with the ICC, implement the Infection Control Assessment Tool (ICAT) to understand current infection control practices. (ICAT is discussed in the next section.)

Where an ICC is not functioning, the DTC (through an Infection Control Subcommittee) can provide basic IC programs and advocate for developing a formal IC program within the hospital setting. Because the consequences of not having a committee are many but the benefits are well known, DTCs have every reason to start an IC program within the available resources of the health care setting.

Adequate training in this field is critical, and DTC members are encouraged to obtain comprehensive education. The Internet has a number of websites for obtaining information and online training (see annex 1). For example, the U.S. Centers for Disease Control and Prevention (CDC) website (www.cdc.gov) provides lists of protocols, and the EngenderHealth (www.engenderhealth.org) has an online training program that can serve as instructional materials for basic IC techniques.

**Infection Control Assessment Tool (ICAT) and Quality Improvement Program, RPM Plus/MSH**

Management Sciences for Health (MSH) has recently developed, through its Rational Pharmaceutical Management (RPM) Plus Program, a tool to assess IC practices and implement interventions to advance practices through a quality improvement (QI) mechanism. The ICAT and quality improvement program provides a standardized approach by combining an IC self-assessment tool (ICAT) and rapid cycle quality improvement (RCQI) (or rapid team problem solving) methods to improve hospital IC practices. RCQI is a quality improvement approach in which a multidisciplinary team collaborates on improving an identified situation. The team identifies and prioritizes areas that need improvement, agrees on specific goals for improvement,
and uses QI (or problem solving) tools to analyze available data about existing systems. The team then develops, tests, and implements a series of focused and affordable changes that can be implemented locally in the system to improve the situation and achieve the agreed-upon goals. The strength of RCQI is in synergizing team ideas in learning about systems and developing appropriate solutions to improve them. The methodology has been applied in various health care settings around the world.

This IC tool also provides resources for quality improvement activities and internationally recognized guidelines for infection control practices.

For more information, contact MSH’s RPM Plus/SPS programs in Arlington, Virginia (e-mail: rpmplus@msh.org; website: www.msh.org/rpmplus).

**Activity 2. Developing Recommendations for Your Facilities or Institutions**

Review the current session and make recommendations for your hospital or primary care clinic for starting an ICC, improving the current committee, or forming an Infection Control Subcommittee of the DTC. Consider these questions—

- What would be the benefits to your hospital if an effective infection control program is started?
- How can your DTC contribute to improving infection control practice within your health-care facility?

**Summary**

Infection control is a critical component in hospitals and primary health care clinics. Likewise, Infection Control Committees are important for both providing the policies and procedures and monitoring the activities of an active IC and prevention program. Many simple, inexpensive strategies can prevent infections.

Ample evidence shows that Infection Control Committees and practices are cost-effective. Cost savings from a decreased rate of nosocomial infections will more than pay for IC activities. By focusing on IC and DTCs, health care systems can lay the foundation for more comprehensive quality improvement programs that will improve patient outcomes.

DTCs can support many IC activities, such as—

- Hand washing and the use of appropriate antiseptics and disinfectants
- Monitoring IV and injection preparation and administration

DTCs should actively promote better use of antimicrobials through the following—

- Guidelines for treatment and surgical prophylaxis
• Selection of appropriate antimicrobials for the formulary
• Antimicrobial use reviews

ICCs, when functioning effectively, will achieve the following—

• Reduce the spread of infectious diseases
• Decrease morbidity and mortality
• Maintain employee health and morale
• Decrease the incidence of AMR
• Decrease health care cost

Annex 1. Internet and CD-ROM Resources: Infection Control Information, Guidelines, and Protocols

**RPM Plus/MSH**


**Centers for Disease Control and Prevention (CDC) Documents and Guidelines**

Centers for Disease Control infection control index:
http://www.cdc.gov/ncidod/dhqp/a_z.html

Hand hygiene:
http://www.cdc.gov/handhygiene/

Guidelines for preventing the spread of TB in hospitals:
http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00035909.htm

Guidelines for surgical site infections:
http://www.cdc.gov/ncidod/dhqp/gl_surgicalsite.html

Improving compliance with hand hygiene:
http://www.cdc.gov/ncidod/eid/vol7no2/pittet.htm

Infection control guidelines for hospital personnel:
http://www.cdc.gov/ncidod/dhqp/gl_hcpersonnel.html

Intravenous catheters:
http://www.cdc.gov/ncidod/dhqp/gl_intravascular.html
Isolation procedures:
http://www.cdc.gov/ncidod/dhqp/gl_isolation.html

Prevention of needle stick infections:
http://www.cdc.gov/niosh/docs/2000-135

“Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis”:  
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm

Urinary catheters:
http://www.cdc.gov/ncidod/dhqp/gl_catheter_assoc.html

Utilizing surveillance data:
http://www.cdc.gov/ncidod/eid/vol7no2/gaynes.htm

Alliance for Patient Safety (World Health Organization)  
(Hand Hygiene and Safe Surgery)

http://who.int/patientsafety  
http://who.int/patientsafety/challenge/en

American International Health Alliance Website

Website and training manuals:  
www.aiha.com

EngenderHealth Website

Online infection control training program:  
http://www.engenderhealth.org/IP/index.html
Session 13.
The Role of the DTC in Containing Antimicrobial Resistance
SESSION 13. ANTIMICROBIAL RESISTANCE

Purpose and Content

Session 13 provides information about the global threat of antimicrobial resistance (AMR) and the role of Drug and Therapeutics Committee (DTC) in containing AMR.

Objectives

After attending this session, participants will be able to—

• Understand the global situation of antimicrobial resistance
• Describe the role of the DTC in containing AMR
• Discuss multifaceted strategies to contain AMR

Preparation and Materials

• Read the Participants’ Guide the evening before the session.

Further Readings


**Introduction**

The use of antimicrobial medicines has greatly contributed to the decline in morbidity and mortality due to infectious diseases over the past half-century. This achievement is being undermined by the rapidly growing problem of AMR. Infectious diseases, such as tuberculosis (TB), sexually transmitted infections, acute respiratory infections, malaria, dysentery, and HIV/AIDS, are becoming increasingly difficult and expensive to treat, and the burden is greatest in developing countries where resources are limited and infection rates are high. The increased costs associated with resistant infections are seriously affecting infectious disease prevention, control, and treatment efforts worldwide and are undermining the gains achieved from health investments.

The factors contributing to AMR are multifaceted and are more evident in resource-constrained countries where problems with pharmaceutical access, quality, management, and use are generally the norm. The increased inflow of HIV/AIDS, TB, and malaria medicines from global
health initiatives has greatly increased the potential for drug resistance in countries with deficient health systems and weak pharmaceutical management capacity, including scarce health professional expertise on AMR and rational antimicrobial use. Although proven tools and approaches exist to improve the management and use of antimicrobials, few AMR advocacy and containment programs are in place at the country level. Awareness about the dangers posed by AMR is generally nonexistent, and relevant pharmaceutical management and AMR interventions are not being implemented.

Global Situation of Antimicrobial Resistance

Drug resistance has emerged across the spectrum of microbes: viruses, fungi, parasites, and bacteria. Major pathogens that have become resistant to antimicrobials include—

- Bacteria causing diverse infections such as *Staphylococci*, *Enterococci*, and *E. coli*
- Agents causing respiratory infections such as *Streptococcus pneumoniae*, TB, and influenza
- Food-borne pathogens such as *Salmonella* and *Campylobacter*
- Sexually transmitted organisms such as *Neisseria gonorrhea*
- *Candida* and other fungal infections
- Parasites such as *Plasmodium falciparum*, the cause of malaria
- The human immunodeficiency virus (HIV), the cause of AIDS

Contributing to the accelerating surge of drug resistance are the ineffectiveness of chloroquine as a primary antimalarial agent, multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), a diversity of antibiotic-resistant diarrheal diseases and acute respiratory infections, HIV/AIDS, and methicillin-resistant *Staphylococcus aureus* (MRSA). Many complex mechanisms of resistance to antifungal medicines have been observed.\(^{25}\) Fluconazole was introduced in the early 1990s as therapy for candidiasis and was rapidly followed by the emergence of fluconazole-resistant oral candidiasis, which is seen in one-third of patients with advanced AIDS.\(^{26}\) The first-line pharmaceutical treatment (chloroquine) for malaria is no longer effective in 81 of the 92 countries where malaria is a major health problem. Penicillin has substantially lost its effectiveness against pneumonia, meningitis, and gonorrhea in many countries. Eighty percent of *Staphylococcus aureus* isolates in the United States are penicillin-resistant and 32 percent are methicillin-resistant.

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The following provides more examples and illustrate the increasing global problem of antimicrobial resistance:\textsuperscript{27}

- Multidrug-resistant \textit{S. enterica} serotype paratyphi (\textit{S. paratyphi}) infections have been associated with an increase in the reported severity of disease and emerged as a major public health problem in Asia.

- Resistance of \textit{Shigella} to ampicillin, tetracycline, co-trimoxazole, and chloramphenicol is widespread in Africa, even through these medicines are still used for first-line chemotherapy for dysentery in many parts of the continent. The introduction of nalidixic acid has been followed by emergence of \textit{Shigella} resistance.

- The emergence and spread of \textit{S. dysenteriae} type I resistant to co-trimoxazole, ampicillin, tetracycline, chloramphenicol, and increasingly nalidixic acid in the past two decades means that these inexpensive and widely available antimicrobials can no longer be used empirically.

- Penicillin and erythromycin resistance is an emerging problem in community-acquired \textit{S. pneumoniae} in Asia, Mexico, Argentina, and Brazil as well as in parts of Kenya and Uganda.

- Widespread resistance of \textit{N. gonorrhea} has necessitated the replacement of penicillin and tetracycline with more expensive first-line medicines, to which resistance quickly emerged. In the Caribbean and South America, azithromycin resistance was found in 16–72 percent of isolates in different locations, resulting in the recommendation that this medicine in turn be replaced by ceftriaxone, spectinomycin, or the quinolones. The high cost of other options, however, such as third-generation cephalosporins makes their use prohibitive in many developing countries.

- Antimicrobial resistance is becoming increasingly common in cholera infections in developing countries. Up to 90 percent of \textit{Vibrio cholerae} isolates are resistant to at least one antimicrobial.

With antimicrobial options becoming limited, physicians in developing countries may have to use older antimicrobial medicines that have become increasingly ineffective, resulting in high rates of treatment failure.\textsuperscript{28} Furthermore, new antibiotics, including second-, third-, and fourth-line choices are much more expensive than the original first-line medicines. In resource-constrained settings, physicians often lack medicine susceptibility testing, or they do not have the option of changing therapies. With the increasing rates of AMR in developing countries, these limitations make their burden even greater.


Hospital settings are an important source of drug-resistant infections. Nosocomial infections occur in up to 10 percent of hospitalized infections. Important bacteria causing nosocomial infections include MRSA, *Enterococcus faecium*, *E. faecalis*, *E. coli*, *K. pneumoniae*, *Enterobacter* spp., *Citrobacter* spp., *Pseudomonas aeruginosa*, and *Acinetobacter calcoaceticus*.

Nosocomial transmission of commonly encountered community acquired, multidrug-resistant organisms, such as pneumococcus, *M. tuberculosis*, *Salmonella* spp, *Shigella* spp, and *V. cholerae*, has been increasingly documented in developing countries. Horizontal transfer of resistant genes from one strain to another can also worsen the possibility of resistant nosocomial infections.

**Impact of AMR**

AMR increases morbidity and mortality in patients with a wide range of diseases. There is a prolonged period of infectiousness with increased risk of transmission of resistant organism. For example, a study of XDR-TB in South Africa in 2006 showed that 52 of 53 identified cases died from the disease. These patients with resistant (and untreated) TB certainly had opportunity to spread this disease to others.

The cost of AMR to the individual as well as society as a whole is enormous. The treatment of MDR TB, for example, is about 300 times more expensive to treat than drug-sensitive TB. The cost of treating MRSA is three times that of methicillin-sensitivity staphylococcus infections. Switching from chloroquine to artemisinin-based combination therapy (ACT) because of resistance comes with an 18-fold increase in cost. The use of second-line antimicrobials to treat resistant infections is not only more expensive, but also can lead to a higher incidence of adverse drug reactions (ADRs).

Antibiotics constitute about 20–40 percent of a hospital’s medicine budget and can lead to significant, unnecessary health care costs, if not carefully managed. Hospital-acquired infections drain precious resources that would otherwise be available for programs to improve access and quality of care.

**Causes of Antimicrobial Resistance**

Of the several key factors that contribute to the emergence and spread of AMR, inappropriate antimicrobial prescribing by health providers and inappropriate self-medication by patients, including poor compliance, are particularly important. Twenty to fifty percent of antimicrobials prescribed for human use may be unnecessary. About half of all antibiotics are used in the

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agricultural sector, not in humans; and forty to eighty percent of antimicrobials for animal use are highly questionable. Additionally, limited access to health care; unregulated availability of medicines; poor quality, substandard, or counterfeit antimicrobials; poor storage conditions; and inadequate infection control in health facilities are several system factors that contribute to the development and spread of AMR.

Several factors contribute to the persistent problem of AMR in the community including cultural conceptions; patient demand for antimicrobials; economic incentives for prescribers and dispensers; influential advertising to consumers, prescribers, and providers by the pharmaceutical industry; and an insufficient level of training among health staff and pharmacists. Poverty and economic hardships that lead to early termination of treatments or sharing of medicines within the family also contribute to the emergence and spread of AMR.

Reasons for inappropriate prescribing include—

- Training deficiencies
- Diagnostic uncertainties
- Formularies and standard treatment guidelines (STGs) not available or not used
- Fear of poor patient outcome and need for self reassurance
- Fear of litigation
- Dispensing prescribers who are motivated by profit to sell more medicines
- Microbiological information not available or not used
- Patient demand
- Financial incentives such as gaining more money through sales of medicines
- Pharmaceutical manufacturers’ influence through inappropriate and biased advertising

**Key Approaches to Containing AMR**

To achieve progress in containing AMR, action is required at all levels of the health care system. Interventions to manage and contain AMR includes AMR advocacy, communications, training programs, research, surveillance, prevention of infectious diseases, improved pharmaceutical quality, improved medicine use, country-level interventions, pharmaceutical regulations, hospital and primary health clinic infection control programs, and improving pharmaceutical management capacity.

A key approach is preserving the effectiveness of existing antimicrobials, which can be achieved by implementing effective DTCs to monitor and control the use of antimicrobials at the hospital and primary health care level.

**Role of the DTC in Containing AMR**

DTCs are important to monitor and improve medicines use in institutional settings and help contain AMR. The World Health Organization (WHO) Global Strategy for Containment of Antimicrobial Resistance stated that DTCs are a key means of intervention to contain AMR in institutional settings. The Second International Conference on Improving Use of Medicines in

33 Ibid.
2004\textsuperscript{34} recommended that DTCs be established at all levels in institutional settings to assist efforts to improve use of medicines and contain costs.

In hospital settings, the DTC is a key body to help preserve effectiveness of existing antimicrobials. This goal can be accomplished by various methods—

- Updating and managing an antimicrobial formulary
- Developing policies on antimicrobial procurement and quality
- Developing and updating antibiotic guidelines and protocols
- Developing antimicrobial policies (e.g., reserve antimicrobials, levels of prescribing, automatic stop orders, and antimicrobial order forms) to improve compliance with antibiotic guidelines and protocols
- Evaluating antimicrobial use based on pre-established criteria of appropriateness and applying remedial measures
- Providing preservice and in-service education on rational use and AMR
- Contributing to collection and management of antimicrobial surveillance and resistance information for coordinated action with the Infection Control Committee
- Providing education to patients on the use and abuse of antimicrobials and encouraging adherence
- Supporting pharmacovigilance activities for antimicrobials

**Interventions to Contain Antimicrobial Resistance**

**Updating and Managing an Antimicrobial Formulary**

The antimicrobial formulary must include agents considered most useful in the context of hospital’s patient population. Efficacy, safety, quality, pharmacokinetic disposition, and cost must all be considered in the decision to add an antimicrobial to the formulary. Duplications within a therapeutic class of antimicrobials should be avoided (e.g., quinolones or third-generation cephalosporins). The DTC or Antimicrobial Subcommittee may apply the techniques discussed in session 2, “Developing and Maintaining a Formulary.”

**Developing Policies on Antimicrobial Procurement and Quality**

The DTC or Antimicrobial Subcommittee can develop relevant policies for antimicrobial procurement and quality. For example, only those antimicrobials that have been approved for the formulary will be routinely procured for the hospital. Nonformulary antimicrobials can still be purchased, but only with permission from the DTC through a nonformulary process. Policies

\textsuperscript{34} http://www.icium.org.
may also be developed for procurement of generic antimicrobials from suppliers with a reliable track record.

**Developing and Updating Antimicrobial Guidelines and Protocols**

In addition to managing the antimicrobial formulary, the DTC or Antimicrobial Subcommittee provides guidelines for the use of both formulary and nonformulary antimicrobials. The hospital pharmacy dispenses the nonformulary antimicrobial only if the medicine is prescribed within these guidelines. For example, guidelines specific to antimicrobial dosage and duration may be developed by the subcommittee for formulary antimicrobials. They can be printed on dosing cards or in a concise, pocket-sized manual.

**Developing Antimicrobial Policies to Improve Compliance with Guidelines**

Multifaceted policies in combination with various approaches can be developed and implemented by the DTC to improve compliance with antimicrobial guidelines and protocols. Providing local evidence, rationale, and benefits of antimicrobial policies is important when seeking consensus from hospital-wide stakeholders so that prescribers do not feel that they are being “policed” by the DTC while implementing antimicrobial policies.

**Levels of Antimicrobial Prescribing Policies**

Prescribing policies should establish three levels of antimicrobials: first-choice, restricted-choice, and reserve.

- **First-choice antimicrobials**—to be prescribed by all doctors

- **Restricted-choice antimicrobials**—for multiple-resistant pathogens, polymicrobial infections, or certain patient conditions that need special attention or more expensive antimicrobials to be prescribed after discussion with head of department

  - Certain antimicrobials can be restricted to particular physician specialties or service areas (e.g., an intensive care unit [ICU]). Restriction may also be applied to certain antimicrobials with broad spectrum of activity.

- **Reserve antimicrobials**—useful for a wide range of infections, but whose use can be restricted because of the need to reduce the risk of developing resistance or because of their relatively high cost

For example, carbapenems (imipenem/meropenem) are broad-spectrum antimicrobials for a majority of gram-positive and gram-negative pathogens. Hospitals try to reserve these antibiotics for use only for special conditions such as resistant nosocomial infections, and they are usually dispensed only after discussion with infectious disease physicians or department heads.
Automatic Stop Orders

The purpose of an automatic stop order is to appropriately limit the duration of antimicrobial usage. This strategy has been used successfully to limit duration of surgical prophylaxis in United Kingdom hospitals. Additionally, stop dates can be used for the use of empiric or therapeutic antimicrobials. The Antimicrobial Subcommittee makes a recommendation to the DTC to authorize stop orders for a list of priority antimicrobials based on dosing and duration of therapy. These steps can be best implemented using antimicrobial order forms (AOFs).

Antimicrobial Order Forms

Rather than the regular prescription form, the AOF is a special preprinted form usually in a different color. Prescribers categorize antimicrobials as prophylaxis, empirical, or therapeutic. For surgical prophylaxis, automatic discontinuation of the antimicrobial takes place usually in the range of 24–48 hours as decided by the institution; for empiric treatment, the suspected cause of infection must be stated; for therapeutic treatment, isolated pathogens and relevant susceptibility is stated. An example of an AOF is provided in figure 1.35

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35 Sital Shah, Chief Pharmacist, Aga Khan University Hospital, Nairobi, Kenya. Former participant of International DTC Training of Trainers course, Malaysia, 2005.
Figure 1. Sample antibiotic order form.
Within the AOF, an automatic stop order policy and list of restricted antimicrobials specific to the individual hospital are provided. Instructions on use of local culture and sensitivity testing are also provided (figure 2).

**Figure 2. Sample instructions in an AOF.**
Intravenous-to-Oral Conversion

Another method to achieve a more rational use of antimicrobials is through an intravenous (IV) -to-oral conversion policy, a widely used method of lowering medicine costs for an institution and its patients. Several advantages have been associated with this method such as less preparation time, lower risks of complications or adverse effects, and potential shortening of the length of hospital stay. The IV-to-oral conversion program involves establishing criteria for conversion, choosing an appropriate antimicrobial, consulting with the relevant physician, and monitoring the patient after conversion. For this policy to be successful, clear guidelines need to be established determining which patients can be converted and which patients should not.

Evaluating Antimicrobial Use Based on Pre-established Criteria of Appropriateness and Applying Remedial Measures

Select high-cost antimicrobials or those that may have the greatest potential for abuse and then conduct a drug use evaluation (DUE) using the techniques described in session 11, “Drug Use Evaluation.” This review is especially useful if the Antimicrobial Subcommittee established guidelines for specific antimicrobials and wants to determine compliance with the guidelines (pre-established criteria). The evaluation may be conducted by reviewing a random sample of prescriptions or case notes over a long period (e.g., 6 to 12 months) or a short study period (e.g., 1 to 3 months) where patients have received the specific antimicrobial.

The data are tabulated, and compliance with various indicators is determined. If noncompliance is observed from the data, a remedial measure may be taken to improve the use of the antimicrobial. The remedial measure may be conducted through variety of methods as described in session 9, “Strategies to Improve Medicine Use—Overview.” After the intervention, a second evaluation is performed to determine the impact of the intervention on the use of the antimicrobial.

Providing Preservice and In-service Education on Rational Use and AMR

Training in the appropriate use of antimicrobials is essential for all health professionals within the hospital or primary health care facility. Regular in-service education programs can improve the use of antimicrobials and decrease the incidence of ADRs as well as decrease overall health care cost. Such education should also be provided at the undergraduate and post-graduate levels and local academic institutions should be encouraged to adopt rational antimicrobial use and AMR concepts in their curriculums.

Liaising with the Infection Control Committee with Regard to the Assessment and Use of Data Obtained from Monitoring AMR

Surveillance of bacterial resistance to antimicrobials is an essential component of any program 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 medicine use behavior. Resistance data not only helps in choosing the correct antimicrobial in individual patient care; if collated, it also allows a DTC to be informed about sensitivity patterns when choosing antimicrobials for the formulary. Many hospital laboratories do not actually collate resistance data to inform the
Resistance is often reported in terms of the number of isolates. Such data, however, usually include multiple specimens from a few very sick patients and does not give an accurate picture of overall resistance in all patients. 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. If surveillance is done, however, quality control within the laboratory is extremely important. Having inaccurate reports is worse than having 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 functional and that all specimen collection and processing are done in a reliable manner.

- **External quality assurance** is accomplished when the laboratory participates in an external scheme run by a reference laboratory. In this situation, 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.

**Providing Education to Patients on the Use and Abuse of Antimicrobials and Encouraging Adherence**

Dispensing pharmacists in the hospital outpatient ward must educate patients on the appropriate use of antimicrobials and encourage adherence. Besides one-to-one education to the patient, the Antimicrobial Subcommittee can create simple poster boards to be placed in the patient waiting area and near the dispensing window. Depending on the institutional context, patient education may also help reduce patients’ unnecessary demands to the provider for an antimicrobial.

**Supporting Pharmacovigilance Activities for Antimicrobials**

Antimicrobial safety and toxicity must be monitored in a coordinated, systematic method. The Antimicrobial Subcommittee may adopt various strategies, as discussed in session 4, “Assessing and Managing Medicine Safety.” Pharmacovigilance for specific antimicrobials with known safety concerns must be designed and implemented. Additionally, antimicrobial use in vulnerable groups such as pediatric and elderly patients may also be monitored. Interventions include dose adjustment in cases of hepatic or renal failure for certain antimicrobials (e.g., aminoglycosides, vancomycin), alertness for allergies (penicillins), and identification of relevant interactions with other medicines (macrolides, azoles). These pharmacovigilance activities will
decrease the incidence of ADRs, decrease the unnecessary use of alternate antimicrobials, and improve the overall use of antimicrobials.

**Establishing An Antimicrobial Subcommittee within a DTC**

Establishing an Antimicrobial Subcommittee within a DTC can help create a task force to design educational and intervention programs to contain the threat of AMR. The Antimicrobial Subcommittee can take leadership in developing policies concerning use of antimicrobials for approval by the DTC and medical staff. The Antimicrobial Subcommittee also has a role in evaluating and selecting antimicrobials for the formulary.

For the Antimicrobial Subcommittee to be successful, clear terms of reference (box 1) and composition of subcommittee must be established. For example, in a private hospital in Kenya, the composition of the Antimicrobial Subcommittee is multidisciplinary, consisting of the following—

- Clinical pharmacist
- Microbiologist
- Nurse representative
- Physician representative
- Chief pharmacist

### Box 1. Terms of Reference for Antimicrobial Subcommittee: Example from Kenya

1. Ensure hospital antibiotics policy is adhered to in the ICU.
2. Promote rational use of antibiotics.
3. Educate the doctors, nurses, and pharmacy staff on appropriate antibiotic usage.
4. Conduct medicine usage review and regular audits.
5. Ensure sensitivity and resistance patterns are determined.

At this hospital, DUE was conducted and showed an overuse of carbapenem antimicrobials. This finding was brought to the attention of the DTC and resulted in guidelines being implemented for the use of these medicines. A substantial decrease in the use of these medicines occurred along with significant cost savings. The DTC also addressed the use of injections in the

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36 Sital Shah, Chief Pharmacist, Aga Khan University Hospital, Nairobi, Kenya. Former participant of International DTC Training of Trainers course, Malaysia, 2005.
outpatient department. Simple indicators studies were employed and resulted in reduced use of injections in the outpatient department along with cost savings on these medicines and the cost to administer.

Other examples of DTC related activities that have led to improved antimicrobial use include the following—

- **AOF**—This form required staff to record the indication for the antimicrobial and an indication if it was treatment or prophylaxis. The implementation of this form has reduced the use of expensive broad-spectrum antimicrobials at a hospital in Nairobi.

- **AOF in Thailand**—This form guided physicians to give explicit information about anatomic and etiologic diagnosis and suspected antimicrobial sensitivity. This action resulted in decreased use of unnecessary antimicrobials and a 30 percent reduction in cost for these medicines.37

- **IV to oral switching of antimicrobials**—This activity, led by the DTC, instituted a program of switching from IV to oral antimicrobials at the earliest possible time to conserve the use IV antimicrobials and to decrease cost. Guideline adherence was encouraged and monitored. This activity resulted in improved use of antimicrobials including a decrease in expensive intravenous medicines.38

**DTC Collaboration with Hospital Departments and Committees**

DTCs can collaborate with other hospital units and departments (figure 3) resulting in synergistic action to contain the threat of AMR with the following—

- Different departments—for education of students, physicians, pharmacists, nurses, and patients

- The Infection Control Committee—to reduce spread of resistant pathogens

- The microbiology department—for collection and management of information on pathogens and resistant patterns

- Hospital management—to develop and implement policies on antibiotic use

- Pharmacy—to improve antimicrobial procurement and quality

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Activity

Each group should discuss and identify a common antimicrobial use problem or issue concerning AMR in its hospitals. The group should then come up with one or more strategies to address these problems. Be prepared to discuss the following questions—

- What strategies will you use to solve the antibiotic use problem? How will you utilize the DTC (if it exists) to lead or support the process?
- How will you monitor your strategy?
- What may be the potential barriers in implementing your strategy?

Summary

Certainly, antimicrobial medicines have greatly contributed to the decline in morbidity and mortality due to infectious diseases over the past half-century. Without effective antimicrobials, infectious diseases would have been devastating to the world’s population.
This achievement is being undermined by the rapidly growing problem of AMR. WHO has identified the DTC as an important intervention mechanism to manage and contain AMR in hospitals. A DTC can do much to contain AMR, such as setting up programs and interventions to identify antimicrobial use problems and implementing specific interventions to improve prescribing, using, and managing antimicrobials.

To be effective, the DTC needs to obtain institutional management and leadership support. Documentation of clinical and economic benefits of the DTC will provide evidence to senior hospital administrators of the vital role the DTC plays in helping to preserve the effectiveness of existing antimicrobials. This effect can be accomplished by multifaceted methods led by the DTC including the following—

- Updating and managing an antimicrobial formulary
- Developing policies on antimicrobial procurement and quality
- Developing and updating antibiotic guidelines and protocols
- Developing policies (e.g., reserve antimicrobials, levels of prescribing, automatic stop orders, and AOFs) to improve compliance with guidelines and protocols
- Evaluating antimicrobial use based on pre-established criteria of appropriateness and applying remedial measures (DUE)
- Providing preservice and in-service education on rational use and AMR
- Liaising with the Infection Control Committee with regard to assessment and use of data obtained from monitoring antimicrobial resistance
- Providing education to patients on the use and abuse of antimicrobials and encouraging adherence
- Supporting pharmacovigilance activities for antimicrobials
Session 14.
Getting Started
SESSION 14. GETTING STARTED

Acknowledgment

This session was adapted from World Health Organization and Management Sciences for Health. 2004. Drug and Therapeutics Committees: A Practical Guide. Geneva: WHO.

Purpose and Content

Session 14 will provide information on the practical methods of getting a Drug and Therapeutics Committee (DTC) started from the beginning or improving a DTC that has only limited activity. Practical applications are discussed, and problems with starting or maintaining a DTC are covered in detail. Solutions to participants’ issues with starting and maintaining a DTC are developed in small groups as well as in a plenary session.

Objectives

After attending this session, participants will be able to—

- Understand the basics of starting a DTC where none exists
- Understand how to improve the functioning of an existing DTC
- Identify and solve management and medicine use problems in establishing and maintaining a DTC

Preparation and Materials

Read the Participants’ Guide.

Addressing the Problem

A DTC must deal with many issues but it cannot address all of them at the same time, especially in the beginning. The way to get started will depend on the various circumstances and context in different countries, health care systems, and hospitals. Many countries do not have DTCs in their hospitals or facilities. Where DTCs do exist, they may 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 medicine 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 medicine use and to work with them in finding the solutions through a DTC.
A Stepwise Approach to Starting a DTC Where None Exists

**Step 1. Do the 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—
  - Prescribing too many medicines
  - Overuse of antibiotics or injections
  - Medication errors
  - Medicines not working
  - Poor quality medicines
  - Adverse drug reactions (ADRs)
  - Frequent medicine stock-outs due to insufficient budget
  - Frequent medicine stock-outs due to poor supply system
  - Medicines not on the formulary list
  - Prescribers not following the formulary list
- Which problem do staff feel is the most serious?
- How does staff think these problems, 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, increase the hospital (or health facility) budget, or both. Discuss how improved use of medicines could lead to improved patient outcomes, decreased costs, or both. 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
- Initial investigation of a medicine use problem to discuss later with medical staff
Step 3. Meet All 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 medicine use data, for example, an ABC analysis that you may have done, following your meeting with senior medical authorities

Then—

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

If prescribers are involved at the start of a project to investigate a medicine use problem, they are more likely to accept the results. In any case, certain detailed investigations such as drug use evaluations (DUEs) cannot be done without the cooperation and participation of senior physicians. Choosing one of the simpler problems for which you can see a solution is wiser than choosing a more complex problem that 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-upon 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 vital, essential, nonessential (VEN) analysis to classify all medicines.
- Conduct an ABC analysis to identify which medicines consume most of the budget (i.e., A medicines).
- Compare the VEN and ABC analyses to see whether any nonessential medicines are in the high cost and consumption A category.

The use of health care facility and hospital indicators may also be useful to measure a medicine use problem.

Step 5. Present Your Findings, and Plan the 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 medicines use problems are identified, discuss the following with the group—

- What do they think of the findings—try to get a consensus from them on which are the most important problems
- How to address the medicine use problems identified; this is your second opportunity to discuss having a DTC
- A plan for a more detailed investigation of the chosen medicine use problem to find out how best to rectify it

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 upon, then solutions can be found by the group. If not, then the group should agree to a process of more detailed investigation (see step 6).

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-upon medicine 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 Medicine Use Investigation**

The type of study will depend on what the medicine 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 or prescriber group and to 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, to do the study.

In a hospital, a DUE of one or two medicines may be done, choosing a medicine according to whether it—

- Has the highest value
- Has serious side-effects
- Is nonessential
- 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 behavior. 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 again 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 medicine use problem before and after implementation. Interventions may be educational, managerial, or regulatory, 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 fewer medicines used because hospital administrators are more likely to be supportive in the future if they see that your measures have saved money. The type of interventions used will depend on the nature of medicine use problem identified and investigated.

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, very likely 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 (TOR), membership, and methods of working need to be agreed upon by the senior physicians and management. A successful DTC is an active one. Therefore, the cycle of changing medicine use problems should be continued, addressing one medicine use problem at a time.
Revitalizing Nonfunctioning DTCs

Many DTCs do not function. Addressing this problem is similar to starting up a DTC from scratch. Often DTCs do not function because there is—

- Lack of awareness of medicine use problems or lack of interest in addressing these problems
- Lack of awareness of what a DTC could do to address medicine 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 step is taken 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 effort will require 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 medicine misuse, for example, the unnecessary cost of using a more expensive branded product that 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-upon set of steps. 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.

See annex 1 for a list of typical problems a DTC faces and recommended solutions.

Activity

Session 14 is designed to develop solutions for participants’ practical problems with starting and maintaining a DTC. These problems may be related to management or clinical issues as they pertain to the DTCs.

Survey forms from the activity in session 1, “Drug and Therapeutics Committee—Overview,” have been analyzed, and one problem per group has been identified and will be assigned. Each group should develop a plan of action to solve the identified problem and present the problem and their proposed solution to the class. Solutions must be practical and feasible.
Each group should work on the assigned problem and prepare a presentation to include—

- A succinct description of the problem and the reasons underlying the problem
- A practical plan of action to solve the problem

**Summary and Conclusion**

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 medicine use problems and then trying to solve them. No single solution or starting point works for every hospital DTC. What you do will depend on your local circumstances. The activities of a DTC should be problem-based, always looking for problems and finding solutions.

Taking over the function of any department is not the role of the DTC. The membership of the DTC should be drawn from the various departments and their expertise used to ensure that all aspects of pharmaceutical 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 a DTC can do to get started. Patients deserve all possible effort to ensure that they receive medicines appropriate to their clinical needs in doses that meet their individual requirements.
Annex 1. Examples of DTC Problems, Causes, and Solutions

<table>
<thead>
<tr>
<th>Problem</th>
<th>Causes</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary list not followed</td>
<td>No formulary list</td>
<td>• Develop a formulary list</td>
</tr>
<tr>
<td></td>
<td>Prescribers do not know about formulary list</td>
<td>• Distribute the formulary list</td>
</tr>
<tr>
<td></td>
<td>Prescribers do not believe in formulary list</td>
<td>• Involve prescribers in development</td>
</tr>
<tr>
<td></td>
<td>Inconsistency between the formulary list and standard</td>
<td>• Educate</td>
</tr>
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<td></td>
<td>treatment guidelines (STGs)</td>
<td>• Review the formulary list to make it</td>
</tr>
<tr>
<td></td>
<td></td>
<td>consistent</td>
</tr>
<tr>
<td>STGs not followed</td>
<td>No STGs exist, or they are outdated</td>
<td>• Develop or revise STGs</td>
</tr>
<tr>
<td></td>
<td>Prescribers do not know about the STGs</td>
<td>• Distribute STGs</td>
</tr>
<tr>
<td></td>
<td>Prescribers do not believe in STGs</td>
<td>• Involve prescribers in the development of</td>
</tr>
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<td></td>
<td>Inconsistency between the STGs and formulary list</td>
<td>STGs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Review the formulary list to make it</td>
</tr>
<tr>
<td></td>
<td></td>
<td>consistent</td>
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<tr>
<td>Frequent medicine stock-outs</td>
<td>Too many medicines used, making it difficult for the</td>
<td>• Review the formulary list to reduce the</td>
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<td></td>
<td>pharmacy to cope</td>
<td>number of medicines available</td>
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<td></td>
<td>Unreliable suppliers</td>
<td>• Review the procurement system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prequalify suppliers</td>
</tr>
<tr>
<td></td>
<td>Overuse of medicines</td>
<td>• Investigate the use of high-consumption</td>
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<tr>
<td></td>
<td></td>
<td>medicines</td>
</tr>
<tr>
<td></td>
<td>Insufficient budget</td>
<td>• Review each therapeutic category in the</td>
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<tr>
<td></td>
<td></td>
<td>formulary and choose the least expensive</td>
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<tr>
<td></td>
<td></td>
<td>therapeutically equivalent alternative</td>
</tr>
<tr>
<td>Medicines not covered by budget</td>
<td>Overuse and irrational use of medicines</td>
<td>• Investigate the use of high-consumption</td>
</tr>
<tr>
<td></td>
<td>Use of overly expensive medicines</td>
<td>medicines</td>
</tr>
<tr>
<td></td>
<td>Use of overly expensive medicines</td>
<td>• Review each therapeutic category in the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>formulary and choose the least expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>therapeutically equivalent alternative</td>
</tr>
<tr>
<td>Medication errors reported</td>
<td>Lack of staff knowledge</td>
<td>• Educate the staff about the error</td>
</tr>
<tr>
<td></td>
<td>Heavy staff workload</td>
<td>reporting system</td>
</tr>
<tr>
<td></td>
<td>Poor lighting and excessive noise</td>
<td>• Review working practices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Arrange for dispensing procedures to take</td>
</tr>
<tr>
<td></td>
<td></td>
<td>place where lighting is good</td>
</tr>
<tr>
<td>Problem</td>
<td>Causes</td>
<td>Solutions</td>
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<td>----------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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<tr>
<td>Poor communication, for example, handwriting and oral orders; prescribers do not know how to write prescriptions properly</td>
<td>and noise is minimal</td>
<td>• Establish protocols for legible handwriting</td>
</tr>
<tr>
<td>Complex calculation needed for prescribing</td>
<td></td>
<td>• Develop or review STGs and the formulary list to simplify the calculations</td>
</tr>
<tr>
<td>Medicines reported not to work</td>
<td>Inappropriate medicine use—prescribing errors or medication errors</td>
<td>• Investigate the clinical use of the medicine</td>
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<tr>
<td></td>
<td>Low medicine efficacy</td>
<td>• Review the literature on the medicine’s efficacy and its inclusion in the formulary</td>
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<tr>
<td></td>
<td>Poor medicine quality as found by visual inspection or testing</td>
<td>• Check quality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Review procurement process and storage</td>
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<tr>
<td></td>
<td></td>
<td>• Consider changing the supplier</td>
</tr>
<tr>
<td>ADRs reported</td>
<td>Inappropriate medicine use—prescribing errors or medication errors reported to have caused an ADR</td>
<td>• Investigate the clinical use of the medicine</td>
</tr>
<tr>
<td></td>
<td>Low medicine efficacy</td>
<td>• Review the procurement process and storage; consider changing the supplier</td>
</tr>
<tr>
<td></td>
<td>True ADR</td>
<td>• Report to the national ADR monitoring center</td>
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<td></td>
<td></td>
<td>• Review the medicine’s safety profile and its inclusion in the formulary</td>
</tr>
<tr>
<td>Overuse and irrational use of medicines</td>
<td>Lack of accepted standards of use</td>
<td>• Develop and implement STGs</td>
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<tr>
<td></td>
<td>Prescriber habit</td>
<td>• Use qualitative methods to investigate prescriber habit, and then design and implement an appropriate intervention</td>
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<tr>
<td></td>
<td>Prescriber lack of knowledge</td>
<td>• Educate the prescribers using face-to-face methods as well as printed materials</td>
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<td></td>
<td>Peer pressure</td>
<td>• Identify the opinion leaders and then involve them in developing and implementing STGs and a DUE</td>
</tr>
<tr>
<td></td>
<td>Patient demand</td>
<td>• Use qualitative methods to investigate patient demand and then design and implement an appropriate intervention</td>
</tr>
<tr>
<td>Patients not getting better</td>
<td>Inappropriate medicine use</td>
<td>• Investigate the clinical use of the medicine used in patients reported to not get better</td>
</tr>
<tr>
<td></td>
<td>Low medicine efficacy</td>
<td>• Review the literature on the efficacy of medicines used in patients not getting better and inclusion of the medicines in the formulary</td>
</tr>
<tr>
<td>Problem</td>
<td>Causes</td>
<td>Solutions</td>
</tr>
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<td>-----------------------</td>
<td>-------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Poor medicine quality | • For patients not improving, review the procurement process and storage of medicines used  
                        | • Consider changing the supplier                                                                |                                                                                                  |
| Wrong diagnosis       | • Educate the prescribers using face-to-face methods as well as printed materials               |                                                                                                |
| 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 or food provided at meetings |
|                       | Nontransparent decision making leading staff to distrust the DTC                                   | • Develop and document TOR 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                           |
|                       | Lack of belief in the need for a DTC                                                                | • Provide evidence of irrational medicine use, the patient harm it causes, and the financial cost |