

Developing pharmacy practice

A focus on patient care

HANDBOOK – 2006 EDITION

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The Hague, The Netherlands

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Cover design by Quim Martell
Designed by minimum graphics
Printed in The Netherlands

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Acknowledgements

The authors are grateful to the following persons who reviewed previous drafts of this document. Their comments were invaluable.

Ms Christal Albert, Cologne, Germany

Dr Rosario d'Alessio, WHO/PAHO, Washington DC, USA

Ms Teresa Alves, FIP Secretariat, The Hague, The Netherlands

Dr Douglas Ball, Department of Pharmacy Practice, Faculty of Pharmacy, Health Sciences Center, University of Kuwait, Kuwait

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Professor Abraham Hartzema, Perry A. Foote Eminent Scholar, Chair in Health Outcomes and Pharmacoeconomics, College of Pharmacy, University of Florida, Gainesville, USA

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Dr Ross Holland, Bowie MD, USA

Dr Adriana Mitsue Ivama, Pan American Health Organization/WHO, Brazil

Dr Nelly Marin Jaramillo, Pan American Health Organization/WHO, Brazil

Dr Richard Thuo Kamau, Nairobi, Kenya

Mr Balkrishna Khakurel, WHO, Kathmandu, Nepal

Dr Rosalyn King, Howard University Continuing Education, Silver Spring MD, USA

Ms Mirjam Kokenberg, Quality Institute for Pharmaceutical Care, Kampen, The Netherlands

Dr Hlonelikhaya Masiza, South Africa Pharmacy Council, Pretoria, South Africa

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Special thanks are due to Ms Monika Zwegarth, School of Pharmacy, University of Limpopo,
South Africa, for her assistance in compiling the document and to Ms Sheila Davey for edit-
ing the text.

WHO expresses appreciation to the United States Agency for International Development for
co-funding this publication.

Foreword

“Pharmacists should move from behind the counter and start serving the public by providing care instead of pills only. There is no future in the mere act of dispensing. That activity can and will be taken over by the internet, machines, and/or hardly trained technicians. The fact that pharmacists have an academic training and act as health care professionals puts a burden upon them to better serve the community than they currently do.”

(From: Pharmaceutical care, European developments in concepts, implementation, and research: a review.^{1,p.x})

This introductory handbook sets out a new paradigm for pharmacy practice. Its aim is to guide pharmacy educators in pharmacy practice, to educate pharmacy students and to guide pharmacists in practice to update their skills. The handbook, which brings together practical tools and knowledge, has been written in response to a need to define, develop and generate global understanding of pharmaceutical care at all levels.

Despite the considerable expertise that went into developing this manual, the World Health Organization (WHO) and the International Pharmaceutical Federation (FIP) consider this first edition as a starting point. The contents will be kept under review as experience is gained from field testing in various countries, continents and in different settings, and will be further developed as more practical information is obtained.

Please contact the WHO Department of Medicines Policy and Standards or FIP to tell us of your experiences with using this manual. We would welcome any comments or suggestions, particularly on the contents and case studies. This feedback will be key to improving future editions of the manual.

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Introduction

Over the past four decades there has been a trend for pharmacy practice to move away from its original focus on medicine supply towards a more inclusive focus on patient care. The role of the pharmacist has evolved from that of a compounder and supplier of pharmaceutical products towards that of a provider of services and information and ultimately that of a provider of patient care. Increasingly, the pharmacist's task is to ensure that a patient's drug therapy is appropriately indicated, the most effective available, the safest possible, and convenient for the patient. By taking direct responsibility for individual patient's medicine-related needs, pharmacists can make a unique contribution to the outcome of drug therapy and to their patients' quality of life. The new approach has been given the name pharmaceutical care. The most generally accepted definition of this new approach is:

"Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life".

(Hepler and Strand, 1990)²

In adopting this definition in 1998, the International Pharmaceutical Federation (FIP) added one significant amendment: *"achieving definite outcomes that improve or maintain a patient's quality of life"*.

The practice of pharmaceutical care is new, in contrast to what pharmacists have been doing for years. Because pharmacists often fail to assume responsibility for this care, they may not adequately document, monitor and review the care given. Accepting such responsibility is essential to the practice of pharmaceutical care.

In order to fulfil this obligation, the pharmacist needs to be able to assume many different functions. The concept of the seven-star pharmacist, introduced by WHO and taken up by FIP in 2000 in its policy statement on Good Pharmacy Education Practice, sees the pharmacist as a caregiver, communicator, decision-maker, teacher, life-long learner, leader and manager.³ For the purposes of this handbook, we have added the role of researcher.

The knowledge base of pharmacy graduates is changing. As these graduates move into practice, so pharmacy practice itself will change, to reflect the new knowledge base. However, pharmacists already in practice were mainly educated on the basis of the old paradigm of pharmaceutical product focus. If these pharmacists are to contribute effectively to the new patient-centred pharmaceutical practice, they must have the opportunity to acquire the new knowledge and skills required for their new role. To do this they must become life-long learners, one of the roles of the new pharmacist.

This handbook is designed to meet these changing needs. It is intended for use not only by pharmacists and interns who already practice in patient care settings, but also by educators and new students – the pharmacists of tomorrow – in countries throughout the world. To reach as wide an audience as possible, the handbook will be available both in electronic form and in print. The aim throughout is to make it interactive and provide suitable "model"

responses, so that it can also be used for self-assessment. It contains a wide variety of illustrative case studies in order to meet the needs of different users. It is designed to guide learners towards specific end-points, enabling them to carry out a task which requires a combination of knowledge, skills and attitudes. These end-points are reflected in the learning objectives provided at the beginning of each section. The handbook has been reviewed by all targeted groups in a wide variety of settings.

Chapter 1 considers some definitions of good pharmacy practice in different contexts. Underpinning them all is the concept of the seven-star pharmacist. **Chapter 2** presents a stepwise approach to pharmaceutical care, within a general practice environment. It also stresses the value of appropriate referral in overall patient care. **Chapter 3** looks at the need to assimilate and manage information and new developments, some trends in evidence-based practice, and the use of guidelines to inform medicine selection within specific contexts. The importance of patient beliefs, preferences, knowledge, rights and choices is also emphasized.

The overarching message of this handbook is that there is an important and rewarding professional role for pharmacists beyond pharmaceutical product supply and management. The pharmaceutical product should be seen not as an end in itself – as often emphasized in pharmaceutical education and practice – but rather as a means to an end. Where medicines are used for the greatest possible benefit of each individual patient and of society as a whole, this will result in improvements in health as well as cost savings. New pharmacists should have the knowledge and skills needed to take up their new role and responsibilities and to function as collaborative members of the health care team.

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PART I

Pharmacists in
the health care team:
a policy perspective

1

New paradigm for pharmacy practice

1.1 Introduction

The number of medicines on the market has increased dramatically over the last few decades, bringing some real innovations but also considerable challenges in controlling the quality and rational use of medicines.

In developing and industrialized countries alike, efforts to provide health care, including pharmaceutical care, are facing new challenges. These include the rising costs of health care, limited financial resources, a shortage of human resources in the health care sector, inefficient health systems, the huge burden of disease, and the changing social, technological, economic and political environment which most countries face. While globalization has brought countries closer together in trade of products and services and in recognition of academic degrees and diplomas, for example, it has led to rapid changes in the health care environment and to new complexities due to increased travel and migration.¹

Access to medicines of assured quality remains a major concern worldwide. One third of the world's population do not yet have regular access to essential medicines.² For many people, the affordability of medicines is a major constraint. Those hardest hit are patients in developing and transitional economies, where 50%–90% of medicines purchased are paid for out-of-pocket. The burden falls most heavily on the poor, who are not adequately protected either by current policies or by health insurance. The logistical aspects of distribution – often seen as the pharmacist's traditional role, especially in health institutions – represents another challenge. Moreover, in many developing countries 10%–20% of sampled medicines fail quality control tests.

A Statement on Ensuring the Quality and the Safety of Medicinal Products to Protect the Patient was jointly signed by FIP and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) in 2000. Its common goal is to protect the well-being of patients in all parts of the world by ensuring that all medicinal products are of good quality and proven safety and efficacy. Both the pharmaceutical industry and the pharmaceutical profession also recognized the need for a regulatory and marketing environment which encourages investment in new innovative medicines and allows their timely introduction and availability to patients worldwide.

Another major challenge is ensuring that medicines are used rationally. This requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.³

However, rational use of medicines remains the exception rather than the rule. For those people who do receive medicines, more than half of all prescriptions are incorrect and more than half of the people involved fail to take them correctly. In addition, there is growing concern at the increase in the global spread of antimicrobial resistance, a major public

health problem. A recent report by WHO⁴ revealed findings of up to 90% resistance to original first-line antibiotics such as ampicillin and cotrimoxazole for shigellosis, up to 70% resistance to penicillin for pneumonia and bacterial meningitis, up to 98% resistance to penicillin for gonorrhoea, and up to 70% resistance to both penicillins and cephalosporins for hospital-acquired *staphylococcus aureus* infections.

In 2000, the FIP Council adopted a Statement of Policy on Control of Resistance to Antimicrobials⁵ which provides a list of recommendations for governments and health authorities on the appropriate measures needed to combat antimicrobial resistance. The statement also declares that pharmacists are ready to collaborate actively with physicians, regulatory authorities and other health professionals in efforts to combat antimicrobial resistance and to participate in public information campaigns on this.

These challenges – both to access to medicines of assured quality and to their rational use – underscore the urgency of the need for global health sector reform. Against this backdrop of ongoing and profound changes in health care delivery systems, a **paradigm shift** in pharmacy practice is occurring. Public health interventions, pharmaceutical care, rational medicine use and effective medicines supply management are key components of an accessible, sustainable, affordable and equitable health care system which ensures the efficacy, safety and quality of medicines. It is clear that pharmacy has an important role to play in the health sector reform process. To do so, however, the role of the pharmacist needs to be redefined and reoriented. Pharmacists have the potential to improve therapeutic outcomes and patients' quality of life within available resources, and must position themselves at the forefront of the health care system. The movement towards pharmaceutical care is a critical factor in this process. While efforts to communicate the correct information to patients are as important as providing the medicine itself,⁶ pharmacists also have a vital contribution to make to patient care through managing drug therapy and concurrent non-prescription or alternative therapies.

Over the past 40 years, the pharmacist's role has changed from that of compounder and dispenser to one of "drug therapy manager". This involves responsibilities to ensure that wherever medicines are provided and used, quality products are selected, procured, stored, distributed, dispensed and administered so that they contribute to the health of patients, and not to their harm. The scope of pharmacy practice now includes patient-centred care with all the cognitive functions of counselling, providing drug information and monitoring drug therapy, as well as technical aspects of pharmaceutical services, including medicines supply management. It is in the additional role of managing drug therapy that pharmacists can now make a vital contribution to patient care.

This chapter describes the new roles, skills and attitudes which pharmacists need to master if they are to become members of multi-disciplinary health care teams, as well as the added benefits which they can provide through their professional input. It also examines the challenges which pharmacists face and the unlimited opportunities available to them to assume leading roles in patient-focused and public health efforts. In some cases, these challenges may involve an expansion of existing roles; in other cases they may require pharmacists to adopt new roles previously considered beyond the scope of traditional pharmacy practice.

1.2 Main learning objectives for Part 1

- Describe the mission of the pharmacy profession to society
- Elaborate on the role of the pharmacist as a member of a health care team
- Describe new perspectives in pharmacy practice
- Define good pharmacy practice in all sectors and settings
- Describe the knowledge, skills and attitudes required for good patient-focused pharmacy practice
- Describe some new roles that pharmacists can assume
- Describe the changes in education and policy necessary to implement patient-focused pharmacy practice.

1.3 What is health?

Pharmacy practice does not take place in a vacuum, but in the health care environment. It aims to improve health. Health is a broad concept which can embody a wide range of meanings from technical to moral and philosophical. It is perhaps the most important human resource.

The most quoted **definition of health** was formulated in the Constitution of WHO in 1946. It is a positive definition which stresses well-being.

“Health is a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity.”
(WHO, 1946)⁷

Over the years, WHO has taken forward the debate and has revised its definition of health.

“Health is the extent to which an individual or group is able, on the one hand, to realise aspirations and satisfy needs; and, on the other hand, to change or cope with the environment. Health is therefore, seen as a resource for everyday life, not an object of living; it is a positive concept emphasizing social and personal resources, as well as physical capacities.”
(WHO, 1984)⁸

There is no single definition that unifies the perceptions about health. Our understanding of it depends on the many different contexts in which life is lived and health is perceived.

Health is a human right and access to health care, including essential medicines, is a derived right. Health is essential for sustainable economic and social development. For example, in many parts of the world, the HIV/AIDS pandemic reduces economic achievements and national health outcomes. Health is thus a very precious resource.

1.4 The pharmacy profession

Medicinal therapy is the most frequently used form of treatment intervention in any health practice setting. Its use has grown dramatically as the population has aged, the prevalence of chronic disease has increased, new infectious diseases have emerged and the range of effective medications has broadened. In addition, more and more so-called “life-style medicines” – treatments for ailments like baldness, dry skin, wrinkles or erectile dysfunction – are being marketed.

Increasingly medicines can be purchased in new settings, and are handled by non-pharmacists. Compounding has been largely replaced by the commercial manufacture of nearly all formulations. Medicines can be bought in supermarkets, in drug stores or at markets. They can also be obtained by mail order or over the Internet, they are sold by medical practitioners and dispensed by computerized dispensing machines.

Under these circumstances it is pertinent to ask the following questions:

Do we still need pharmacists?

What is the value of pharmacy services?

Professions exist to serve society. Hence the mission of the pharmacy profession must address the needs of society and individual patients. At one time, the acts of deciding on drug therapy and implementing it were relatively simple, safe and inexpensive. The physician prescribed and the pharmacist dispensed. However, there is substantial evidence to show that the traditional method of prescribing and dispensing medication is no longer appropriate to ensure safety, effectiveness and adherence to drug therapy. The consequences of medicine-related errors are costly in terms of hospitalizations, physician visits, laboratory tests and remedial therapy. In developed countries, 4%–10% of all hospital in-patients experience an adverse drug reaction – mainly due to the use of multiple drug therapy, especially in the elderly and patients with chronic diseases. In the USA, for example, it is the 4th–6th leading cause of death and is estimated to cost up to US\$130 billion a year. Elsewhere, in the UK it accounted for £466 million (over US\$812 million) in 2004. In 1998, FIP published a Statement of Professional Standards on Medication Errors Associated with Prescribed Medication which aims to define the term “medication error” and to suggest a standard nomenclature to categorize such errors and their severity. The Statement also makes recommendations to members of the health care delivery system designed to improve safety in the manufacturing, ordering, labelling, dispensing, administration and use of medicines.

While appropriate drug therapy is safer and more cost-effective than other treatment alternatives, there is no doubt that the personal and economic consequences of inappropriate drug therapy are enormous. It is important for society to be assured that spending on pharmaceuticals represents good value for money. In view of their extensive academic background and their traditional role in preparing and providing medicines and informing patients about their use, pharmacists are well positioned to assume responsibility for the management of drug therapy.

The accountability of health professionals for their actions is another major issue in health care provision. In the traditional relationship between the doctor as prescriber and the pharmacist as dispenser, the prescriber was accountable for the results of pharmacotherapy. That situation is changing in rapidly evolving health systems. The practice of pharmaceutical care assumes the pharmacist to be responsible for patients under their care, and society will not only accept that assumption but hold the profession to it.

At the same time, other professions such as medical doctors, nurses and medical and pharmacy assistants also acquire competence and feel confident to function as drug therapy managers. In some countries they are moving aggressively to do so. Pharmacy students and practitioners must be educated to assume the responsibility for managing drug therapy, so that they can maintain and expand their position in the health care system and are compensated for their role in providing pharmaceutical care.

Dispensing is, and must remain, a responsibility of the pharmacy profession. While fewer pharmacists may be actually engaged in dispensing medication, predominantly in rural areas, more pharmacists will be managing the dispensing process and assuming responsibility for its quality and outcomes.

While change may generate potential threats, it can also open up immense opportunities. The pharmacy profession has a responsibility to identify new opportunities for pharmacy practice in a changing health sector context, to assess and to test them, and to demonstrate their ability to implement them successfully.

1.5 New dimensions of pharmacy practice

1.5.1 Pharmaceutical care

Pharmaceutical care is a ground-breaking concept in the practice of pharmacy which emerged in the mid-1970s. It stipulates that all practitioners should assume responsibility for the outcomes of drug therapy in their patients. It encompasses a variety of services and functions – some new to pharmacy, others traditional – which are determined and provided by the pharmacists serving individual patients. The concept of pharmaceutical care also includes emotional commitment to the welfare of patients as individuals who require and deserve pharmacists' compassion, concern and trust. However, pharmacists often fail to accept responsibility for this extent of care. As a result, they may not adequately document, monitor and review the care given. Accepting such responsibility is essential to the practice of pharmaceutical care.

Pharmaceutical care can be tendered to individuals and populations. "Population-based pharmaceutical care" uses demographic and epidemiological data to establish formularies or medicine lists, develop and monitor pharmacy policies, develop and manage pharmacy networks, prepare and analyse reports of drug utilization/costs, conduct drug utilization reviews and educate providers on medicine policies and procedures.

Without individual pharmaceutical care, however, no system can manage drug therapy and monitor medicine-related illness effectively. The population-based functions identified above need to occur either before or after patients are seen and provide valuable information, but cannot replace patient-specific services while patients are being seen. Medicine-related illnesses occur frequently even with medicines that are in a system's formulary or medicines list, since these medicines are often prescribed, administered or used inappropriately. Patients need pharmacists' services at the time they are receiving care. Successful pharmacotherapy is specific for each patient. It includes individual drug therapy decisions, reaching concordance (an agreement between the patient and the health care provider on the therapeutic outcome and how it may be achieved), and critical patient monitoring activities. For each individual patient's drug treatment, the pharmacist develops a care plan together with the patient. Patients can then contribute to successful outcomes by taking part of the responsibility for their own care and not relying solely on caregivers, in the former paternalistic style. A stepwise approach to patient care is described in detail in Chapter 2.

Pharmaceutical care does not exist in isolation from other health care services.⁹ It must be provided in collaboration with patients, physicians, nurses and other health care providers. Pharmacists are responsible directly to patients for the cost, quality and results of pharmaceutical care.

In 1998, a Statement of Professional Standards in Pharmaceutical Care was adopted by FIP. It provides guidance to pharmacists and national health care organizations as they

begin to implement broad pharmaceutical services in their countries. FIP supports the concept of pharmaceutical care but recognizes the individual needs of different countries.

1.5.2 Evidence-based pharmacy

In an increasingly complex health care environment, it has become difficult to compare the effectiveness of different treatments. Health care interventions can no longer be based on opinion or individual experience alone. Scientific evidence, built up from good quality research, is used as a guide, and adapted to each individual patient's circumstances. This approach is further described in detail in Chapter 3.

1.5.3 Meeting patients' needs

In patient-centred health care, the first challenges are to identify and meet the changing needs of patients. Pharmacists need to ensure that people can access medicines or pharmaceutical advice easily and, as far as possible, in a way and at a time and place of their own choosing. They can empower patients by engaging them in dialogue to communicate knowledge which enables them to manage their own health and treatment. Although patients are exposed to a wide range of information from package inserts, promotional materials, advertising in the media and through the Internet, this information is not always accurate or complete. The pharmacist can help informed patients to become accurately informed patients by offering unbiased relevant evidence-based information and by pointing to reliable sources. Counselling on disease prevention and lifestyle modification will promote public health, while shared decision-making on how to take medicines through a concordant approach will optimize health outcomes, reduce the number of medicine-related adverse events, cut the amount of medicine which is wasted and improve adherence to medical treatment.

In 2000, a publication by the UK Department of Health entitled "Pharmacy in the Future"¹⁰ set out the requirement for structured professional support to be provided by pharmacists, to improve and extend the range of pharmacy services available to patients, including identification of the individual's pharmaceutical needs, development of partnerships in medicines taking, coordination of repeat prescribing and dispensing processes, targeted treatment review and follow-up. This approach may also provide a model for the future of pharmacy elsewhere. A new contractual framework for community pharmacy is being implemented that is key to delivering the vision of primary care in the future. This new community pharmacy contract will enable reorientation of services to meet patient expectations and maximize pharmacist potential to deploy their skills to better effect. The pharmacy contract provides for categorization into essential, advanced and enhanced pharmacy services with a focus on quality and outcome in all cases.¹¹

1.5.4 Chronic patient care – HIV/AIDS

Throughout history the world has never faced a health challenge like the HIV/AIDS pandemic. In order to respond adequately, health systems, especially in resource-limited settings, are undergoing a shift in health care provision from acute health care services to chronic patient care. With an estimated 40 million people living with HIV worldwide and 3 million people dying of AIDS in 2004 alone, the HIV/AIDS pandemic represents an extraordinary human, human rights and humanitarian crisis and a tragedy of immense social, economic and public health impact.¹² In 2004, the world's nursing, medical and pharmacy leaders issued a resolution stating that all health professionals should commit the neces-

sary funds and resources to rise to the challenge of HIV/AIDS.¹³ Health professionals, including pharmacists, should also act as strong advocates and social leaders.

The availability of financial resources for the provision of antiretroviral therapy (ART) in resource-limited settings is steadily increasing. The United Nations Declaration of Commitment on HIV/AIDS¹⁴ and the World Health Organization's announcement declaring HIV/AIDS to be a global public health emergency¹⁵ underscore the urgent need for scaling up ART in resource-limited settings. In 2003, WHO made a commitment to treat 3 million people by the end of 2005.¹⁶ More recently, in July 2005 leaders of the G-8 nations committed to the goal of scaling up access to HIV/AIDS treatment, care and prevention services with a view to moving towards universal access to ART by 2010.

Human resources are the most critical component of health systems and delivery. However, in many of the communities where ART is urgently needed, there is a significant shortage of skilled human resources to provide routine health care. People with many different skills (including management, administration, supply management, clinical care and community-based care) are needed for the safe and effective delivery of ART. Successful outcomes in delivering ART have relied on strategies to reduce dependence on highly skilled health professionals by sharing aspects of patient care and follow-up among different cadres of health care workers, the community and family members. To address the lack of highly skilled human resources, existing skills should be upgraded to cope with the demands of delivering ART and care services. Strategies will depend on health sector policies and the chosen service delivery approach.

One of the key health professionals that must be mobilized and involved is the pharmacist. Pre-service and ongoing training of pharmacists in providing HIV/AIDS prevention, care and treatment is essential. The content and delivery of training for pharmacists will depend on their allocated roles and responsibilities. Since pharmacists' knowledge, attitudes and behaviour influence the way in which HIV care, treatment and prevention services are delivered and used, adherence to chronic HIV/AIDS care and treatment is one of the key areas where pharmacists need to be involved.

In 2003, the FIP Council adopted a Statement of Professional Standards on the Role of the Pharmacist in Encouraging Adherence to Long Term Treatments. There are many reasons for seeking to improve adherence to long-term therapies for chronic diseases such as HIV/AIDS. The benefits include better health outcomes and improved quality of life and improved safety for the patient, as well as cost savings for all stakeholders. Pharmacists and other health professionals providing services involving treatment with medicines should make every effort to assist patients who wish to do so to improve adherence to their treatments.

In 1997, the role of pharmacists in efforts to combat HIV/AIDS was acknowledged in a joint Declaration by FIP and WHO. In 2004, FIP launched an International Network for Pharmacists on HIV/AIDS (www.fip.org/hiv aids) which focuses on three main areas: training, documentation and exchange of experience. It includes training modules, policy documents, useful publications, links to relevant national and international organizations, an events calendar to which additional events can be added, and a mailing list to allow pharmacists to exchange points of view and experiences. This network will help to link up pharmacists throughout the world working in the field of HIV/AIDS and will help pharmacists to become leaders in the battle against the pandemic.

1.5.5 Self-medication

In 1996, a Statement of Principle, entitled Self-Care (including Self-Medication): The Professional Role of the Pharmacist, was adopted by the FIP Council. It sets out FIP's policies regarding the responsibilities of pharmacists concerning advice on self-medication. Areas covered by the statement include pharmacy premises, sales promotion, advice on the treatment of symptoms, specific requests for medicines (i.e., by name), referral notes and confidentiality. This Statement was followed in 1999 by a joint Declaration on Responsible Self-Medication which was signed by the FIP Council together with the World Self-Medication Industry (WSMI). This provides guidance to pharmacists, patients and the industry regarding the safe and effective use of non-prescription medicines.

BOX 1.1 THE PHARMACIST'S EXPANDING ROLE

As the experts in medicines, pharmacists have always been known as an accessible and trusted source of advice and treatment. Today, their contribution to health care is developing in new ways to support patients in their use of medicines and as a part of clinical decision-making across the range of specialisms.

Pharmacies are open all day, are convenient for most people to get to and there is no need for an appointment to see the pharmacist. All this makes pharmacies the natural first port of call for help with common ailments.

Self-treatment of common ailments is becoming more popular as a growing range of safe, effective medicines becomes available from the pharmacy without the need for a doctor's prescription. Pharmacists have the expertise to advise both on the choice of medicines and their safe and effective use. The right choice of self-treatment can prevent some conditions from developing or help others clear up more quickly.

Adapted from: What we do. Royal Pharmaceutical Society of Great Britain. Available at: http://www.rpsgb.org.uk/public/pharmacists/what_we_do/index.html

1.5.6 Quality assurance of pharmaceutical care services

A basic concept which should underlie all health care services and pharmacy practice is that of assuring the quality of patient care activities. Donabedian defined the three elements of quality assurance in health care as being structure, process and outcome.¹⁷ The processes used in the various settings of pharmacy practice all comply with the same principles, although they may differ in application. They will be described in detail in this handbook. Quality assurance processes of pharmaceutical care services serve to contribute towards better patient outcomes.

Definitions of the quality assurance of pharmaceutical care should encompass both technical standards and patients' expectations. While no single definition of health service quality applies in all situations, the following common definition is a helpful guide:

"Quality assurance is that set of activities that are carried out to monitor and improve performance so that the health care provided is as effective and as safe as possible".

(Quality Assurance Project, 1993).¹⁸

Quality assurance can also be defined as "all activities that contribute to defining, designing, assessing, monitoring, and improving the quality of health care". These activities can be performed as part of the accreditation of pharmacies, supervision of pharmacy health workers, or other efforts to improve the performance and the quality of health services.

The Quality Assurance Project of the Center for Human Sciences in Bethesda, USA, lists four core principles which have emerged to guide quality assurance in health care:

1. Focus on the client/patient
2. Focus on systems and processes
3. Focus on measurement
4. Focus on teamwork

The implementation and practice of pharmaceutical care must be supported and improved by measuring, assessing and improving pharmacy practice activities, utilizing the conceptual framework of continuous quality improvement. A key lesson is that in many cases quality of pharmacy services can be improved by making changes to the health care system or pharmacy system without necessarily increasing resources. Improving the processes of pharmacy practice not only creates better outcomes but also reduces cost through eliminating waste, unnecessary work and repetition of work already done. Thus quality improvement must address both the resources (structures) and activities carried out (processes) to ensure or improve the quality of pharmaceutical care (outcomes).

1.5.7 Clinical pharmacy

The term “clinical pharmacy” was coined to describe the work of pharmacists whose primary job is to interact with the health care team, interview and assess patients, make specific therapeutic recommendations, monitor patient responses to drug therapy and provide medicines information. Clinical pharmacists work primarily in hospitals and acute care settings and provide patient-oriented rather than product-oriented services.

In some countries, the pharmacy profession has evolved to the point at which clinical pharmacy with patient-focused practice is no longer the exception but the rule for most pharmacists. Yet clinical pharmacy is still practiced exclusively in in-patient settings and hospitals, where access to patient data and the medical team is available.

The medical record, also known as the patient chart or file, is a legal document including hospital-specific admission information, initial patient history and physical examination, daily progress notes made by health care professionals who interact with the patient, consultations, nursing notes, laboratory results, diagnostic procedures, dietary recommendations, radiology and surgery reports. Most charts also include sections for medication orders and clinical pharmacy progress notes on pharmacokinetic dosing and other relevant therapeutic comments and recommendations.

Clinical pharmacy requires an expert knowledge of therapeutics, a good understanding of disease processes and a knowledge of pharmaceutical products. In addition, clinical pharmacy requires strong communication skills with solid knowledge of the medical terminology, drug monitoring skills, provision of medicines information, therapeutic planning skills and the ability to assess and interpret physical and laboratory findings.¹⁹

Pharmacokinetic dosing and monitoring is a special skill and service provided by clinical pharmacists. Clinical pharmacists are often active members of the medical team and accompany ward rounds to contribute to bedside therapeutic discussions.

The impact of clinical pharmacy services has been well documented in in-patient settings, and to a lesser extent in ambulatory and community settings. The value and acceptance of clinical pharmacy services were first documented in the 1970s and 1980s.

In the USA, many schools of pharmacy have introduced curricula requiring all pharmacy students to study clinical pharmacy, leading to a professional Doctorate of Clinical Pharmacy.

1.5.8 Pharmacovigilance

Medicines safety is another important issue. Because of intense competition among pharmaceutical manufacturers, products may be registered and marketed in many countries simultaneously. As a result, adverse effects may not always be readily identified and so are not monitored systematically. Pharmacovigilance is a structured process for the monitoring and detection of adverse drug reactions (ADRs) in a given context.²⁰

Data derived from sources such as Medicines Information, Toxicology and Pharmacovigilance Centres have great relevance and educational value in the management of the safety of medicines. Medicine-related problems, once detected, need to be assessed, analysed, followed up and communicated to regulatory authorities, health professionals and the public. Pharmacovigilance includes the dissemination of such information. In some cases, medicines may need to be recalled and withdrawn from a market, a process that entails concerted action by all those involved at any point in the medicines supply chain. Pharmacists have an important contribution to make to post-marketing surveillance and pharmacovigilance. More information on this is provided on the WHO website at: <http://mednet2.who.int/mdra/default.htm>

1.6 The value of professional pharmacist services

Through its impact on individual patients' state of health, pharmaceutical care improves the quality and cost-effectiveness of health care systems. Improvements at the micro-level impinge on the overall situation at the macro-level, i.e., communities benefit when individuals within them enjoy better health. Ultimately the population at large will also benefit as system-wide improvements occur.

Pharmacists' services and involvement in patient-centred care have been associated with improved health and economic outcomes, a reduction in medicine-related adverse events, improved quality of life, and reduced morbidity and mortality.^{21,22} These accomplishments have been achieved through gradual expansion of traditional roles and, in some cases, through the emergence of collaborative drug therapy management programmes. Nonetheless, the potential for pharmacists to effect dramatic improvements in public health remains largely untapped.

A recent review investigated the effectiveness of professional pharmacist services in terms of consumer outcomes, and where possible, the economic benefits. Its key findings illustrate the value of a range of services, including continuity-of-care after hospital discharge and education to consumers and to health practitioners. Overall, this review demonstrates that there is considerable high quality evidence to support the value of professional pharmacy services in improving patient outcomes or medication use in the community setting. Elsewhere, an Australian study on the economic impact of increased clinical intervention rates in community pharmacy found that adequately trained and remunerated pharmacists generated savings (on health care, medicines and pharmacy practice costs) six times greater than those of a control group with no access to the same education or remuneration. It was estimated that adequately trained and remunerated pharmacists would save the health care system 15 million Australian dollars (approx. US\$100 million) a year.²³ Similar findings are reported from the USA.²⁴

An adequate level of remuneration for pharmacists is key to ensuring that they move towards good pharmacy practice, and in particular towards pharmaceutical care. However, efforts to ensure that pharmacists are adequately recompensed will require effective documentation of what pharmacists actually do to improve outcomes as well as agreement by funders that what they do has economic value.

1.6.1 The Pharmacy Practice Activity Classification (PPAC)

As pharmacists increasingly focus their practices on the provision of pharmaceutical care and expect to be compensated for pharmaceutical care services, the need for a consistent and broadly accepted classification of pharmacy practice activities becomes evident. Although many systems exist to record pharmacists' activities, until now the profession has lacked a widely accepted way to describe or document these activities in a common language. The Pharmacy Practice Activity Classification (PPAC)²⁵ initiated by the American Pharmacists Association (APhA) provides a common language that, if used consistently, will yield comparable data among studies. This in turn can contribute to building databases for statistically sound determinations about pharmacists' patient-centred activities and whether they improve patient outcomes and the use of resources. Such systems are already used by other health professions (e.g., medicine, nursing). An important purpose of the PPAC is to provide a solid foundation to support systems for remuneration that can be used for billing.

The PPAC is focused primarily on activities of licensed, practicing pharmacists across the continuum of health care settings. The classification captures a range of activities from traditional dispensing to direct patient care services. It is recognized that pharmacists occupy other roles – in the pharmaceutical industry, administration, regulatory agencies, professional associations, public health, academia – that are not directly related to patient care. The benefits of consensus on a uniform classification system include:

- advancing the recognition of pharmaceutical care as a key component of pharmacy practice, leading to an understanding of the value of and need for compensation for the delivery of pharmaceutical care services

Table 1.1 The Pharmacy Practice Activity Classification

A. Ensuring appropriate therapy and outcomes
A.1 Ensuring appropriate pharmacotherapy
A.2 Ensuring patient's understanding/adherence to his or her treatment plan
A.3 Monitoring and reporting outcomes
B. Dispensing medications and devices
B.1 Processing the prescription or medicine order
B.2 Preparing the pharmaceutical product
B.3 Delivering the medication or device
C. Health promotion and disease prevention
C.1 Delivering clinical preventive services
C.2 Surveillance and reporting of public health issues
C.3 Promoting safe medication use in society
D. Health systems management
D.1 Managing the practice
D.2 Managing medications throughout the health system
D.3 Managing the use of medications within the health system
D.4 Participating in research activities
D.5 Engaging in interdisciplinary collaboration

- increasing interdisciplinary links and encouraging collaboration with other health care professionals, by defining common goals and patient interventions
- facilitating and standardizing research directed towards establishing the value of services in optimizing patient care
- supporting pharmacists to better manage their practices
- assisting in developing quality assurance systems and quality of care guidelines for practices
- facilitating documentation of pharmaceutical care activities in computer-based patient record systems.

1.7 The pharmacist as a member of the health care team

The health care team consists of the patient and all the health care professionals who have responsibility for patient care. This team needs to be well defined, and collaboration needs to be actively sought. Pharmacists have an important role to play in this team. They will need to adapt their knowledge, skills and attitudes to this new role, which integrates traditional pharmaceutical science with clinical aspects of patient care, clinical skills, management and communication skills, active collaboration with medical teams and solving of medicine-related problems.

If they are to be recognized as full members of the health care team, pharmacists will need to adopt the essential attitudes required by health professionals working in this area: visibility, responsibility, accessibility in a practice aimed at the general population, commitment to confidentiality and patient orientation. Pharmacists will need to be competent and possess both vision and a voice to fully integrate themselves into the health care team.

The World Health Professions Alliance was established in 1999 to facilitate close collaboration between FIP, the World Medical Association (WMA), International Council of Nurses (ICN) and World Dental Federation (FDI) in support of governments, policy-makers and WHO in order to better deliver cost-effective quality health care worldwide (www.whpa.org). Through this alliance, over 20 million health care professionals can be reached worldwide, providing a valuable source of knowledge and experience.

1.7.1 Pharmacy practice settings

The role of the pharmacist takes different forms in various parts of the world. The pharmacist's involvement with pharmaceuticals can be in research and development, formulation, manufacturing, quality assurance, licensing, marketing, distribution, storage, supply, information management, dispensing, monitoring or education. Supply and information management activities have been termed "pharmaceutical services" and continue to form the foundation of pharmacy practice.

Pharmacists practice in a wide variety of settings. These include community pharmacy (in retail and other health care settings), hospital pharmacy (in all types of hospital from small local hospitals to large teaching hospitals), the pharmaceutical industry and academia. In addition, pharmacists are involved in health service administration, in research, in international health and in nongovernmental organizations (NGOs).

1.7.2 Levels of practice and decision-making

Pharmacy practice takes place at different levels. The ultimate aim of activities at all these levels is to benefit patients by improving and maintaining their health.

Activities at individual patient level comprise all aspects of providing and managing a patient's drug therapy (i.e., pharmaceutical care, including clinical pharmacy services). At this level, decisions are made on issues of pharmaceutical care and triage (i.e., prioritization of care, patient follow-up and therapeutic outcome monitoring).

Some of the activities at the level of supply management²⁶ in community and hospital pharmacy such as manufacture, compounding, procurement and distribution of medicines are seen as routine or "back office" activities and are not discussed in this handbook. However, these activities remain important, as the availability of medicines of assured quality at affordable prices is a prerequisite for any pharmaceutical care. For official recognition and reimbursement for interventions in the health care system, pharmacists usually need to comply with a wide range of rules relating to health care. Important aspects include terminology, standards, documentation, responsibility and accountability.

At the level of an institution, such as a hospital, clinic, managed care organization or pharmacy, tools used for medicines selection include formularies, standard treatment guidelines and medicines utilization reviews. These tools are typically developed by Drug and Therapeutics Committees²⁷ or by National Essential Medicines Committees. The development process is no longer confined to the developing group, but involves professionals at all levels and is increasingly based on clinical evidence rather than isolated expert opinions. These tools should be accepted by individual health care providers and should be implemented.

At the system level (e.g., at national, federal, state or district level), planning, management, legislation, regulation and policy are the enabling environment in which any health care system develops and operates. The system level also includes standards of practice and mandates for pharmacy that are managed at national, federal, regional, state or district level depending on the country. National medicines policies²⁸ have become an integral part of many countries' national health policies. At the international level, there are moves to harmonize approaches worldwide – an approach that warrants greater attention in view of the global reach of the pharmaceutical industry and pharmacy practice.

At community and population level, pharmaceutical practice comprises the activities which support the other levels (i.e., information, education and communication to promote public health, the provision of medicines information, research, dissemination of new information, education and training of staff, consumer groups, community-based organizations and health system researchers).²⁹

Health promotion, disease prevention and lifestyle modification are activities at community level that have a public health focus. Pharmacists can offer public health interventions more conveniently than other groups since they are easily accessible and recognized as experts in matters of health. Pharmacists are a trusted source of information and advice on health and medicines. However, they cannot operate in isolation and must accept joint responsibility with all health professionals to serve community and public health goals.

1.7.3 The seven-star pharmacist

To be effective health care team members, pharmacists need skills and attitudes enabling them to assume many different functions. The concept of the "seven-star pharmacist" was

introduced by WHO and taken up by FIP in 2000 in its policy statement on Good Pharmacy Education Practice to cover these roles: caregiver, decision-maker, communicator, manager, life-long learner, teacher and leader.³⁰ For the purposes of this handbook we have added the function of the pharmacist as a researcher.

The roles of the pharmacist are described below and include the following functions:

- **Caregiver:** Pharmacists provide caring services. They must view their practice as integrated and continuous with those of the health care system and other health professionals. Services must be of the highest quality.
- **Decision-maker:** The appropriate, efficacious, safe and cost-effective use of resources (e.g., personnel, medicines, chemicals, equipment, procedures, practices) should be the foundation of the pharmacist's work. At the local and national levels, pharmacists play a role in setting medicines policy. Achieving this goal requires the ability to evaluate, synthesize data and information and decide upon the most appropriate course of action.
- **Communicator:** The pharmacist is in an ideal position to provide a link between prescriber and patient, and to communicate information on health and medicines to the public. He or she must be knowledgeable and confident while interacting with other health professionals and the public. Communication involves verbal, non-verbal, listening and writing skills.
- **Manager:** Pharmacists must be able to manage resources (human, physical and financial) and information effectively; they must also be comfortable being managed by others, whether by an employer or the manager/leader of a health care team. More and more, information and its related technology will provide challenges as pharmacists assume greater responsibility for sharing information about medicines and related products and ensuring their quality.
- **Life-long-learner:** It is impossible to acquire in pharmacy school all the knowledge and experience needed to pursue a life-long career as a pharmacist. The concepts, principles and commitment to life-long learning must begin while attending pharmacy school and must be supported throughout the pharmacist's career. Pharmacists should learn how to keep their knowledge and skills up to date.
- **Teacher:** The pharmacist has a responsibility to assist with the education and training of future generations of pharmacists and the public. Participating as a teacher not only imparts knowledge to others, it offers an opportunity for the practitioner to gain new knowledge and to fine-tune existing skills.
- **Leader:** In multidisciplinary (e.g., team) caring situations or in areas where other health care providers are in short supply or non-existent the pharmacist is obligated to assume a leadership position in the overall welfare of the patient and the community. Leadership involves compassion and empathy as well as vision and the ability to make decisions, communicate, and manage effectively. A pharmacist whose leadership role is to be recognized must have vision and the ability to lead.

And the added function of:

- **Researcher:** The pharmacist must be able to use the evidence base (e.g., scientific, pharmacy practice, health system) effectively in order to advise on the rational use of medicines in the health care team. By sharing and documenting experiences, the pharmacist can also contribute to the evidence base with the goal of optimizing patient care and outcomes. As a researcher, the pharmacist is able to increase the accessibility of

unbiased health and medicines-related information to the public and other health care professionals.

1.8 Pharmacy practice: a commitment to implement change

1.8.1 Policy changes

The first WHO Consultative Groups on the Role of the Pharmacist met in New Delhi in 1988 and in Tokyo in 1993.³¹ In 1994, the 47th World Health Assembly called for the development and implementation of national medicines policies aimed at improving access to and rational use of medicines. National medicines policies, which have been developed in over 100 WHO Member States, provide a framework for good pharmaceutical practice. The WHO Revised Drug Strategy relating to the role of the pharmacist was also addressed in the 1994 resolution of the World Health Assembly.³² This resolution recognizes the key role of pharmacists in public health, including the use of medicines. It emphasizes their responsibility to provide informed and objective advice on medicines and their use, to promote the concept of pharmaceutical care, and to participate actively in illness prevention and health promotion. The third and fourth WHO consultative groups on the role of the pharmacist met in Vancouver in 1997³³ and in The Hague in 1998.³⁴

Other documents on good pharmaceutical practice include the WHO document “Good Pharmacy Practice (GPP) in Community and Hospital Pharmacy Settings”³⁵ and the FIP documents “Guidelines for Good Pharmacy Practice” of 1993, revised in 1997,³⁶ and “Good Pharmacy Practice in Developing Countries: Recommendations for stepwise implementation.”³⁷

FIP has issued statements on professional standards for continuing professional development, good pharmacy education practice³⁸ and pharmaceutical care.³⁹

Although many countries have already established their own good practice guidelines, the levels of knowledge about them, the ways in which they are used and monitored, and the ways in which practitioners learn how to apply them vary tremendously. This handbook is designed to help improve this situation.

1.8.2 A change in pharmacy education and a new learning approach

Pharmacists stand at the interface between research and development, manufacturer, prescriber, patient and the medicine itself. WHO has called for greater involvement of pharmacists in the general health care system and wider use of their broad academic background. In its statement of policy, FIP says that the changes in the pharmacist’s role must be reflected in the basic and continuing education of pharmacists,⁴⁰ with a greater focus on student learning. The new paradigm for pharmacy requires that pharmacists are far more than experts in pharmaceutical chemistry and pharmaceuticals. They have to understand and apply the principles behind all the activities necessary to manage drug therapy. In 1999, the European Association of Faculties of Pharmacy (EAFFP) proposed a shift during the pharmacy study programme from laboratory-based sciences to practice and clinical sciences.⁴¹

The movement towards the patient care approach has occurred to varying degrees in some countries such as the UK and the USA.^{42–45} It encompasses care in its widest application, i.e., the opportunity for pharmacists to change and improve patient outcomes as integral, active members of the patient care team. However, pharmacy curricula have long been neglected at many learning institutions, which has helped perpetuate the undervalued sta-

tus of pharmacists in the health care sector, particularly in developing countries. In traditional pharmacy curricula, the emphasis is often on the technical aspects of pharmacy, rather than on professional practice.

The forces behind the changes in pharmaceutical education are many and varied, and increasing in both number and intensity. The major economic and political forces affecting the health care system in most countries are also having an impact on the practice of pharmacy. As a result, radical changes are needed in pharmaceutical education. The role and function of pharmacists and pharmaceutical staff need to be reappraised and the educational outcomes of the evolving pharmacy curriculum should be clearly defined. The use of outcomes statements will help to drive curriculum development. Educational outcomes can be used as a new organizing framework that integrates science, professional attributes, interprofessional practice, and professionalism across new major headings of pharmaceutical care, systems management, and public health, as they are in the practice of pharmacy. Education outcomes should include the following:

- Pharmaceutical care with provision of both patient-centred care and population-centred care
- Systems management of resources (human, medical, informational and technological) and medication use systems
- Public health assuring effective and quality health and prevention services and developing public health policy.

The educational change will require not only extensive curriculum revision and restructuring, but also a major commitment to faculty development to prepare teachers to educate pharmacists in a different way. The type and depth of didactic and experiential material to be included will be different. The amount and allocation of educational resources will have to change. Schools and colleges of pharmacy should create, establish and evaluate practice models that could be used within evolving health care environments.⁴⁶ Courses should take into consideration the needs of the target audience, learning outcomes, course content, teaching methods, learning resources, participant assessment, course evaluation, and quality assurance when being introduced into the curriculum.⁶

In recent years, there has been a shift in health sciences education towards a problem-based learning approach. Problem-based pharmacy curricula have been introduced at universities in a number of countries, including the UK, Australia, the Netherlands and South Africa. In some countries, outcome competencies (Unit Standards) have been defined against which practice may be compared. These standards are used to assess health professionals' knowledge and skills in pre-registration examinations or in continuing professional development (CPD). CPD, including research and reflection on the outcomes of actions, contributes to the maintenance of life-long competency to practice. In its statement on CPD, FIP establishes a framework within which pharmacists can meet this obligation.

These are times of enormous change in health care and in the pharmacy profession. At no time in its recent history has the profession been faced with such challenges and opportunities. While the profession should articulate pharmaceutical care as the major contribution it has to offer to society, pharmaceutical education needs to develop the outcomes, competencies, content and process of the educational curriculum that is required to prepare students to render pharmaceutical care at the entry points in the health care system.

1.9 Summary

Although the number of pharmaceutical products on the market is increasing, access to essential medicines is still lacking in many parts of the world. Rising health care costs and changing social, technological, economic and political environments have made health care reforms necessary throughout the world. New approaches are needed at individual and at population level to provide safe and effective pharmacotherapy to patients in an ever more complex environment.

Pharmacists are in an excellent position to meet the need for professionals to assure the safe and effective use of medicines. To do so, pharmacists must assume greater responsibility than they currently do for the management of drug therapies for the patients they serve. This responsibility goes well beyond the traditional dispensing activities that have long been the mainstay of pharmacy practice. While supervision of the routine medicines distribution process must remain the responsibility of pharmacists, their direct involvement in medicine distribution will decrease, since these routine activities will be handled by qualified pharmacy assistants. However, the number of supervisory activities will increase. Thus, pharmacists' responsibilities must be expanded to include monitoring therapeutic progress, consulting with prescribers, and collaborating with other health care practitioners on behalf of patients. The movement towards pharmaceutical care is a critical factor in this process.

The value of pharmacists' services in terms of clinical, economic and social outcomes has been documented. The Pharmacy Practice Activity Classification (PPAC) initiated by the American Pharmacists Association (APhA) provides a common language for a consistent classification of pharmacy practice activities that represents a new way to describe or document pharmacists' activities in a common language.

Pharmacy is practiced across a range of both traditional and new settings and levels of decision-making. As members of the health care team, pharmacists need to be able to assume many different functions. The concept of the seven-star pharmacist was introduced by WHO and FIP to describe these roles.

Pharmacists have the potential to improve therapeutic outcomes and patients' quality of life within available resources, and must position themselves appropriately within the health care system. Pharmaceutical education has a corresponding responsibility to produce graduates who are competent to deliver pharmaceutical care. Outcome competencies contribute to quality assurance by providing readily accessible standards against which practice may be measured.

Self-assessment questions: (see Appendix 3 for model answers)

1. In what ways has pharmacy practice changed over the past 40 years?
2. List the roles of the "seven-star pharmacist".
3. Differentiate between the terms pharmaceutical practice, pharmaceutical services and pharmaceutical supply.
4. Identify the three components of quality assurance in health care in your working environment.

Additional self-assessment topics

For your own working environment:

1. Describe the role and function of the pharmacist in public health.
2. Elaborate on the role of the pharmacist in HIV/AIDS.
3. Explain the benefits of a uniform pharmacy practice activities system.
4. Identify changes that must be implemented to assume the new roles of pharmacy practice.

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PART II

Pharmacists in
patient care: a practice
perspective

2

Pharmaceutical care

2.1 Introduction

Part 1 has provided the necessary background with which to approach the implementation of pharmaceutical care. This chapter provides guidance on the process of delivering pharmaceutical care in a general practice environment.

Pharmacists provide professional services in a variety of settings in response to local, national and international needs and priorities, with a focus on populations and/or individual patients. **Pharmaceutical public health** includes services to populations, such as local guidelines and treatment protocols, medicine use review and evaluation, national medicine policies and essential medicines lists, pharmacovigilance, needs assessment and pharmaco-epidemiology. Pharmaceutical public health has been defined as:

“The application of pharmaceutical knowledge, skills and resources to the science and art of preventing disease, prolonging life, promoting, protecting and improving health for all through the organised efforts of society.”

(Walker R, 2000).¹

In contrast, **pharmaceutical care** is delivered at the individual patient level. This concept was first defined as:

“The care that a given patient requires and receives which assures safe and rational drug usage.”

(Mikeal et al., 1975).²

Since 1975 there have been many changes to this definition, but the one that lays a foundation for this chapter is that attributed to Hepler and Strand (1990).³

“Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient’s quality of life”.

In 1998, FIP adopted this definition with one significant change – amending it to read *“improve **or maintain** a patient’s quality of life”*. This is probably a more realistic goal, particularly for chronic progressive diseases such as HIV/AIDS and diabetes where maintenance of quality of life would itself be a significant achievement.

The practice of pharmaceutical care is new, in contrast to what pharmacists have been doing for years. The key words are “responsible provision” and “definite outcomes”. Whether pharmacists are reviewing a prescription or a patient medication record, talking to a patient or responding to symptoms, they are automatically assessing needs, prioritizing and creating a plan to meet those needs. What they often fail to do is to accept responsibility for this care. Consequently they may not adequately document, monitor and review the care given. Accepting such responsibility is essential to the practice of pharmaceutical care.

The practice of pharmaceutical care makes explicit the pharmacist’s responsibility to the patient for the prevention of medicine-related illness. In this practice, the pharmacist

evaluates a patient's medicine-related needs, then determines whether one or more drug therapy problems exist, and, if so, works with the patient and other health care professionals to design, implement and monitor a care plan. This plan should be kept as simple as possible, and may refer to relevant sections of national or local evidence-based guidelines.⁴ The care plan would aim to resolve the actual drug therapy problems and prevent potential drug therapy problems becoming a reality.

A drug therapy problem is defined as:

“An undesirable event, a patient experience that involves, or is suspected to involve drug therapy, and that actually or potentially, interferes with a desired patient outcome”.

(Cipolle et al., 1998)⁵

Ideally pharmaceutical care should be provided to all patients in receipt of pharmaceutical services. However, in practice this is not always possible due to limited resources and pharmacists may have to prioritize particular patients in such situations. The term **triage** designates a system whereby a group of casualties or other patients is sorted according to the seriousness of their injuries or illnesses so that treatment priorities can be allocated between them. In emergency situations it is designed to maximize the number of survivors.

Occasionally the pharmaceutical public health role may be in conflict with the pharmaceutical care role at individual patient level. In a public health context pharmacists aim to do the greatest good for the greatest number of people, which may prejudice the care of an individual in resource-limited settings.

In this chapter a systematic approach to the delivery of pharmaceutical care is set out, involving the following four steps:

- **Step 1: Assess the patient's drug therapy needs and identify actual and potential drug therapy problems**
- **Step 2: Develop a care plan to resolve and/or prevent the drug therapy problems**
- **Step 3: Implement the care plan**
- **Step 4: Evaluate and review the care plan**

In addition, the pharmacy services required to resolve a patient's drug therapy problems are discussed.

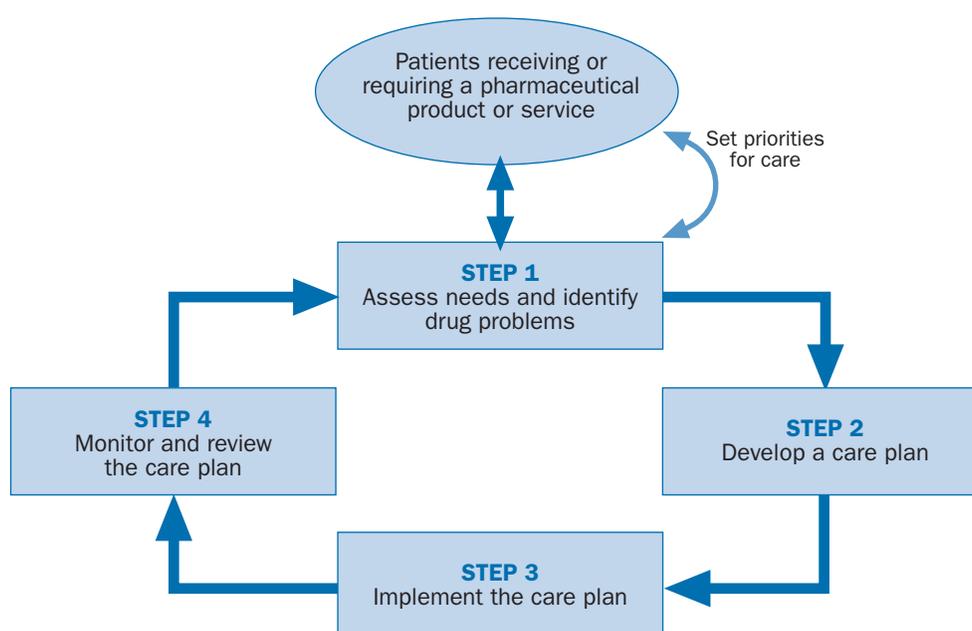
2.2 Main learning objectives

- Describe the concept of pharmaceutical care
- Discuss the term drug therapy problem, providing examples relevant to your own practice
- List the main steps in the pharmaceutical care process and indicate how they contribute to Good Pharmaceutical Practice
- List the main elements of a pharmaceutical care plan
- Describe the therapeutic follow-up and outcome monitoring required to facilitate continuity of care
- Discuss mechanisms for identifying priorities for pharmaceutical care in resource-limited environments and identify one priority specific to your own practice.

2.3 The pharmaceutical care process

The delivery of effective pharmaceutical care to patients requires pharmacists to practice in a way that uses their time effectively and reflects their responsibility and accountability. Ideally all patients who receive pharmaceutical products or services should also receive pharmaceutical care. Pharmacists should assume that all patients require pharmaceutical care until they have been assessed to exclude drug therapy problems (Step 1). However, due to limited resources, this step is not always possible and a systematic approach (see Figure 2.1 below) may need to be adopted to facilitate the targeting of care. Prioritization is used routinely in health care, especially in resource-constrained environments, to ensure that services are targeted particularly to those patient groups and individual patients who need them most. Targeting may occur prior to Step 1 or as part of Step 1 depending on available resources.

Figure 2.1 A systematic approach to the delivery of pharmaceutical care



(Adapted from Clinical Resource and Audit Group, 1996)⁶

LEARNING ACTIVITY 2.1

Outline the concept of pharmaceutical care and discuss how it differs from your current practice.

→ Step 1: Assess the patient's drug therapy needs and identify actual and potential drug therapy problems

Good communication needs to be established with the patient, carer and other members of the health care team at the outset in order for pharmacists to collect, synthesize and interpret the relevant information. When pharmacists assess patients, they must take full account of all patient and medication factors that may predispose patients to the risk of drug therapy problems. The assessment process involves talking to patients, carers or

representatives and consulting other members of the health care team, as well as reviewing patient medication and clinical records. Although the focus is on drug therapy problems, the process allows the identification of disease-related problems as the therapeutic approach is verified and validated. In addition, opportunities for health promotion and preventive health care are identified and incorporated within the plan.

ILLUSTRATIVE CASE STUDY – CASE 2.1

Mrs W, a 53-year-old woman has had gastrointestinal acid-related disorders (GORD) diagnosed by endoscopy. Mrs W has a history of asthma, hypertension and duodenal ulcer (DU). Her current drug therapy includes amlodipine (10mg in the morning), salbutamol inhaler (two puffs as required), beclometasone inhaler (200mcg twice daily), and theophylline (300mg twice daily). Mrs W has recently undergone successful *H. pylori* eradication therapy, which has been confirmed by carbon urea breath test. Mrs W smokes 10 cigarettes a day, has a body mass index of 35 and does not drink alcohol.

Identify lifestyle, medicine and disease factors for the above patient:

1. Lifestyle factors

- She is obese and should try to lose weight.
- She is a smoker. Nicotine can cause reflux by reducing lower oesophageal sphincter tone.
- Other factors may exist but are not apparent from the history. For example, she does not drink alcohol but may drink an excess of coffee or other beverages such as colas or tea, which would exacerbate GORD due to their caffeine content.

2. Drug factors

- Calcium channel blockers reduce lower oesophageal sphincter tone which can lead to acid reflux. Perhaps the amlodipine could be changed to another anti-hypertensive such as bendroflumethiazide (bendrofluazide).
- Theophylline also reduces lower oesophageal sphincter tone. Review asthma management. If appropriate, could stop theophylline without adding on therapy or replace theophylline with another drug such as salmeterol.

3. Disease factors

- Diagnosis of GORD may have been masked by long term treatment of DU which has recently been healed by *H. pylori* eradication; this is not uncommon.
- 'Atypical' presentations of GORD include asthma symptoms linked to acid reflux.

This systematic process allows the pharmacist to identify actual or potential drug therapy problems as illustrated in the following case study.

ILLUSTRATIVE CASE STUDY – CASE 2.2

Mrs P, aged 74 years, has recently been diagnosed with Parkinson's disease. Her only medical condition listed is angina. Her current drug therapy is as follows:

glyceryl trinitrate (GTN) 500mcg	one tablet sublingually as required
haloperidol 0.5mg capsules	one capsule three times daily.

Identify drug therapy problems for this patient and indicate whether they are actual or potential problems.

Drug therapy problems identified in case 2.2

Type of drug therapy problems	Description
1. Needing pharmacotherapy but not receiving it – actual problem	Antiplatelet prophylaxis indicated for angina – low-dose aspirin daily
2. Needing pharmacotherapy but not receiving it – potential problem	Review need for prophylactic anti-anginal therapy by monitoring GTN usage and frequency of anginal attacks. Also check cholesterol level and initiate therapy if required.
3. Taking or receiving a medicine with no valid indication – actual problem	Review need for haloperidol. No indication recorded in notes nor identified from patient interview.
4. Experiencing an adverse drug reaction (ADR) – potential problem	Stop haloperidol and review diagnosis of Parkinson's disease

LEARNING ACTIVITY 2.2

Discuss the term drug therapy problem and provide six examples relevant to your own practice. Examples of drug therapy problems have been reproduced in the table below to facilitate your response. Please enter examples against the types of problems presented.

Provide six examples of drug therapy problems

Type of drug therapy problems	Example
Needing pharmacotherapy and not receiving it (a drug indication)	
Taking or receiving the wrong drug	
Taking or receiving too little of the correct drug	
Taking or receiving too much of the correct drug	
Experiencing an adverse drug reaction	
Experiencing a drug-drug or drug-food interaction	
Not taking or receiving the drug prescribed	
Taking or receiving a drug for no valid indication	

Categories of drug therapy problems

Cipolle et al (1998) proposed the following categories of drug therapy problems:

1. Appropriate indication for the medication: patient either requires drug therapy or is receiving unnecessary drug therapy.

Needing drug therapy but not receiving it

- Untreated indication – e.g. primary essential hypertension untreated with e.g. thiazide diuretic
- Failure to give additional drug therapy for an existing condition – e.g. hypertension poorly controlled because of failure to add a beta-blocker to the thiazide
- Failure to give prophylactic therapy – e.g. low-dose aspirin as anti-platelet prophylaxis in ischaemic heart disease (IHD)

Receiving unnecessary drug therapy

- No medical indication present – e.g. antibiotics for viral infections
- Addictive/recreational drug use – e.g. heroin, cocaine, amphetamines
- Non-drug therapy more appropriate – e.g. coronary artery bypass grafting in severe angina
- Duplicate drug therapy – e.g. transdermal nitrate patches and oral nitrates
- The drug is being used to treat an avoidable adverse drug reaction – e.g. levodopa prescribed for movement disorder caused by metoclopramide when domperidone could be prescribed instead

2. The most effective medication: the patient is receiving the wrong medicine or the dosage is too low.

Receiving the wrong medicine

- Dosage form inappropriate – e.g. sustained release antihypertensive drug in patient with a colostomy
- Contraindication present – e.g. beta-blocker administered to an asthmatic
- Condition refractory to drug – e.g. high-dose inhaled steroids in patients with chronic obstructive pulmonary disease (COPD) who are not responsive to steroids
- Drug not indicated for condition – e.g. non-steroidal anti-inflammatory drugs (NSAIDs) given long term for osteoarthritis with no inflammation present when simple analgesic would be effective
- More effective drug available – e.g. statins more effective than fibrates for primary hyperlipidaemia

Dosage too low

- Wrong dose – e.g. low dose of ACE inhibitor in heart failure when patient could benefit from a higher dose
- Existing tolerance – e.g. caused by failure to observe 8-hour nitrate-free period
- Duration inappropriate – e.g. 3-day course of antibiotics for COPD patient with recurrent chest infection
- Loss of efficacy due to incorrect storage – e.g. interrupted cold chain for vaccines
- Incorrect administration – e.g. poor inhaler technique
- Reduced absorption due to drug interaction – e.g. chelation of tetracycline and iron

3. The safest medication: is the patient taking or receiving too much of the correct drug or is the patient experiencing a clinically significant adverse drug reaction?

Too much of the correct drug

- Dosage too high for indication – e.g. 5 mg bendroflumethiazide for hypertension
- Wrong dose – e.g. more than 4 g of paracetamol per day for an adult
- Duration inappropriate – e.g. 10-day course of antibiotics for an uncomplicated urinary tract infection (UTI)
- Increased serum levels due to drug interaction – e.g. theophylline and ciprofloxacin leading to theophylline toxicity

Adverse drug reactions

- Unsafe drug for patient – e.g. oral contraceptives for patient with history of deep vein thrombosis (DVT)
- Allergic reaction – e.g. anaphylaxis with penicillin
- Drug interaction – e.g. beta-blockers and verapamil causing atrioventricular (AV) block
- Dosage increase too fast – e.g. phenytoin dose increase (zero order kinetics)
- Undesirable effect – e.g. ototoxicity with aminoglycosides

4. Patient adherence and convenience

Examples

- Product not available – local or national supply problems
- Product not affordable to the patient or the government health service
- Medicine cannot be swallowed – stroke patient with dysphagia
- Instructions not understood, remembered or even agreed by the patient
- Medicine not taken - health beliefs, cultural or other reasons.

Self-care (where patients purchase medicines over the counter) is an important component of all health care systems. Unfortunately it may be the only form of access to medicines in countries unable to sustain a publicly-funded health service. It is just as important for pharmacists to provide pharmaceutical care for such patients who may be at greater risk of drug therapy problems due to limited medical supervision of therapy.

ILLUSTRATIVE CASE STUDY – CASE 2.3

Mrs L, a 59-year-old patient, asks to purchase 'high strength' ranitidine for her 'ulcer'. From her records you note that she has no recorded history of peptic ulcer disease. Further discussion with Mrs L reveals that she has been purchasing ranitidine, which has had little effect. She attributed this to the low strength she has been purchasing over the counter hence her request for the 'high strength' ranitidine. Her symptoms are rather vague and include upper abdominal discomfort, nausea and occasional vomiting associated with recent weight loss. Her only medical condition is pernicious anaemia for which she is receiving hydroxocobalamin injections every three months.

Identify drug therapy problems for the above patient and identify whether they are actual or potential.

Unnecessary therapy (ranitidine) (actual) up-referral required.

The patient has pernicious anaemia in which lack of gastric intrinsic factor due to an autoimmune gastritis causes malabsorption of vitamin B12, hence the need for hydroxocobalamin injections. This condition is also associated with hypo-acidity and an increased risk of gastric cancer. Such patients invariably have no parietal cells and therefore cannot produce gastric acid and so medicines such as ranitidine are inappropriate. This case merits further specialist investigation and an urgent up-referral should be made.

→ Step 2: Develop a care plan to resolve and/or prevent drug therapy problems

Not all patients may progress to Step 2. For example, no problems may have been identified at Step 1 or you may not be able to meet the needs of a particular patient due to severe resource limitations. If the latter is the reason the drug therapy problems identified should be documented and brought to the attention of the patient and the health care team and advice provided for reasons of ethical, clinical and professional responsibility, even if the patient cannot be followed up.

Prioritize drug therapy problems

Once identified (Step 1), drug therapy problems should be prioritized within the context of the overall clinical management of the patient as illustrated in the following case study.

ILLUSTRATIVE CASE STUDY – CASE 2.4

Mr D, aged 52 years, has been diagnosed with hyperlipidaemia and advised on diet and lifestyle measures for the past year. His medical history includes hypertension and atrial fibrillation (AF). His blood pressure was recently measured as 140/85 mm Hg, pulse 40 beats per minute and a lipid screen showed total cholesterol of 8.4 mmol/L. On interview the patient complains of tiredness and weight gain. Current drug therapy is as follows:

amiodarone	200 mcg in the morning
bendroflumethiazide	10 mg in the morning

Drug therapy problems identified in Case 3.4

Type of drug therapy problem	Description	Priority
1. Taking or receiving too much of the correct drug – potential problem	High dose thiazide may contribute to hyperlipidaemia – reduce dose, counsel patient and monitor blood pressure (BP)	Low
2. Experiencing an adverse drug reaction – potential problem	Symptoms may be suggestive of hypothyroidism due to amiodarone therapy – check triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH)	High
3. Needing pharmacotherapy and not receiving it – actual problem	Patient has AF and is at considerable cardiovascular risk – statin indicated to reduce cholesterol to 5 mmol/l or less	Low
4. Needing pharmacotherapy and not receiving it – actual problem	Warfarin indicated for treatment of AF – initiate therapy, counsel and monitor the international normalized ratio (INR)	Medium

In this case the top priority would be to establish if the patient is hypothyroid and treat accordingly. In addition, the patient has significant cardiovascular risk, which can be reduced by commencing warfarin treatment. The hyperlipidaemia and bendroflumethiazide

dose reduction have a lower priority until the potential thyroid disorder is dealt with, as the latter can influence the lipid profile and total lipids.

Identify desired therapeutic objectives and proposed actions

A statement should be made of what the pharmacist intends to achieve for a patient in relation to each drug therapy problem. The statements should be agreed with the patient and the health care team. These therapeutic objectives should be expressed as measurable outcomes to be achieved within a defined time scale.

In deciding on the most appropriate actions it is vital that the pharmacist confirms the acceptability of these actions with the patient. If a number of options exist, the patient must be given sufficient information to select the most appropriate option.

Develop a monitoring strategy

A monitoring strategy should be identified to measure progress towards achievement of the therapeutic objectives. This strategy should be agreed with the patient and other members of the health care team and should be undertaken at specified intervals and for a defined period prior to further review.

Document the care plan

The pharmacist's record of drug therapy problems and therapeutic objectives, together with the proposed actions, form a documented **pharmaceutical care plan**. Good documentation facilitates continuity of care and clinical audit.

→ Step 3: Implement the care plan

The pharmaceutical care plan is implemented with the agreement of the patient and, where possible, within the context of the overall care of the patient, in cooperation with other members of the health care team.

ILLUSTRATIVE CASE STUDY – CASE 2.5

Mrs J, aged 45 years, has recently been diagnosed with asthma, following reversibility testing with a short-acting bronchodilator. Her relevant medical history includes osteoarthritis and hypertension. Her blood pressure was recently measured as 170/110 mmHg. Mrs J smokes 30 cigarettes a day, is a moderate to heavy drinker and does no physical exercise. Previous drug therapy of bendroflumethiazide 2.5 mg in the morning was ineffective for hypertension. Her current drug therapy is as follows:

Paracetamol	500 mg 2 as required up to 8 in 24 hours
Propranolol	40 mg three times daily
Salbutamol metered dose inhaler (MDI)	2 puffs as required
Budesonide turbo (dry powder inhaler)	200 mcg twice daily

Case 2.5: Development of pharmaceutical care plan

Description of drug therapy problem	Priority	Therapeutic objectives	Proposed actions
1. Potential adverse drug reaction (ADR) to propranolol	High	Avoidance of ADR and attainment of normal lung function – immediately	Stop propranolol
2. Ineffective therapy – hypertension	High	BP target 140/85 mmHg	Discuss options for anti-hypertensive therapy with patient. Lifestyle changes shown to reduce blood pressure include reduced alcohol intake, reduced weight if obese, reduced salt intake and regular physical exercise. Overall cardiovascular risk may be further reduced by stopping smoking
3. Potentially no valid indication for asthma therapy	High	Normal lung function and withdrawal of unnecessary therapy – immediately	Measure the peak expiratory flow rate (PEFR) and perform reversibility test with beta agonist after stopping propranolol
4. Not receiving the prescribed drug due to inappropriate drug delivery	Medium	Good inhaler technique and effective therapy- delay until beta-blocker has been withdrawn and diagnosis of asthma confirmed	MDI and turbo inhaler have different inhalation techniques. If patient can cope with MDI, change all inhalers to MDI to improve technique

After such a care plan has been agreed with the patient and the health care team, each should sign the documentation as part of the overall quality management system and to facilitate clinical audit.

→ Step 4: Evaluate and review the care plan

Actual outcomes are evaluated in relation to the therapeutic objectives to determine whether drug therapy problems have been resolved. If outcomes are not achieved, the care plan should be reviewed. The actual outcomes may then be accepted as being the best achievable for the patient, or an alternative plan may be necessary. The plan should develop as original drug therapy problems resolve and new drug therapy problems appear, which require resolution.

Illustrated case study 2.5 continued

Therapeutic objectives	Outcomes	Revision to plan
1. Avoidance of ADR and normal lung function – immediately	Propranolol stopped and PEFR returned to normal – ADR confirmed	Problem resolved. Record ADR in case notes to ensure beta blocker is not administered in the future
2. Normal lung function and withdrawal of unnecessary therapy – immediately	Reversibility test confirmed normal peak flow with no additional benefit to PEFR after administration of salbutamol	Problem resolved. Remove asthma diagnosis from patient history
3. Good inhaler technique and effective therapy – delay until beta-blocker has been withdrawn and diagnosis of asthma confirmed	Not actioned – no longer relevant	Problem resolved
4. BP target 120/80 with no side-effects – within three months	Actual BP 145/90 mmHg, patient confirmed compliance with therapy	Add another antihypertensive after discussion with patient and health care team – amlodipine 5mg in the morning, counsel patient and recheck BP in 4 weeks

LEARNING ACTIVITY 2.3

Identify three patients from your own practice and follow the four steps above using the documentation provided in the appendix. Discuss your pharmaceutical care plans with one or more colleagues at regular intervals, and use the review process to identify your personal training and Continuing Professional Development (CPD) needs.

2.4 Pharmaceutical services

Strand et al (1992) used the term pharmaceutical services to represent all the services that pharmacists require to resolve a patient's drug therapy problems. These services range from the provision of medicines information to patient counselling to medicines distribution. Clearly, medicines information pharmacists who provide comprehensive, current and accurate information based on best evidence are supporting the delivery of pharmaceutical care, although they themselves are not actually delivering it. Patient counselling services should be incorporated into standard daily interaction with patients in the community pharmacy setting.⁷ Similarly, timely and accurate drug distribution is required to ensure the delivery of pharmaceutical care.

2.5 Referral

The roles of the seven-star pharmacist require them to participate as a member of the health care team. In providing pharmaceutical care the pharmacist has to facilitate the continuity of care. As part of providing pharmaceutical care it may be necessary for a pharmacist to refer patients to other health care providers. In doing so it is essential to guarantee continuity of care for the patient. Health care needs could range from obtaining a prescription at a more convenient place to seeking additional treatment. For this purpose, the pharmacist may need to refer a patient to other members of the health care team or to other health care institutions. While formal referral by pharmacists is uncommon practice in many parts of the world, in many countries pharmacists are the first contact for advice on health-related issues and have a good relationship with the community. This relationship places a pharmacist in an ideal position to identify and refer social and health-related issues. A formal referral system involving different health care providers will strengthen the pharmacist's professional position with other care providers.

Referring the patient to a health care provider or health care institution for more specialized care than is available in the current health care setting is referred to as up-referral e.g., from a primary health care facility or community pharmacy to a medical doctor or hospital. Down-referral is where it may be appropriate to refer a patient to a less specialized care facility e.g., from a hospital to a primary health care clinic or community pharmacy. In providing pharmaceutical care it is necessary to address the patient's medicine-related needs through a holistic approach, which may require referring a patient for social counselling to a social worker, religious leader, traditional healer, complementary practitioner or counsellor.

This chapter has described the development of a pharmaceutical care plan based on the patient's drug therapy-related problems or needs. Difficulty experienced by the patient in obtaining his or her prescribed medicines should also be seen as a medicine-related problem. As part of Step 2 in the pharmaceutical care process the pharmacist may identify actions which require referral. As part of the care plan the pharmacist has to determine the specific nature of the referral. The patient's health care need could fall outside the scope of practice of a pharmacist, the need for a medicine prescription or making a definite diag-

nosis. Patient factors, e.g., to decrease travel cost for repeat prescriptions, could also be a need for referral. The pharmacist is responsible for communicating the referral with the health care worker or institution. This communication may be written or verbal and should contain the following information:

- a short summary of the patient's medical history
- a short description of the current medical problem
- description of the need for referral
- description of the patient's current therapy
- the pharmaceutical care plan if necessary.

Up-referral

The pharmacist is, in many instances, the first contact for advice regarding different ailments, injuries and other health care issues. In providing pharmaceutical care the pharmacist is responsible for identifying medicine-related problems and developing a pharmaceutical care plan for a patient. As part of the pharmaceutical care plan it may be necessary for the pharmacist, regardless of his or her practice site, to refer a patient for specific or specialized care. The scope of pharmaceutical practice, the pharmacist expertise and severity of the patient's condition should guide the decision for up-referral.

ILLUSTRATIVE CASE STUDY – CASE 2.6

Mr H brings his 12-year-old son, Alex, to the pharmacy to buy dressings for a wound on the boy's leg. You notice that the wound is still fresh and bleeding. On questioning you find out that a stray dog has bitten the boy. You realize that the wound may need to be sutured and that the boy needs prophylactic antibiotics and tetanus and rabies vaccines to prevent complications. You refer the patient to the 24-hour emergency clinic in the area and explain to Mr H that his son will be given the recommended treatment at the clinic.

Management objectives at clinic

- avoid infections – prophylactic antibiotics
- prevent tetanus – tetanus prophylaxis
- prevent rabies – determine the need for rabies vaccine and or rabies immunoglobulin
- avoid disability and scar formation
- pain relief.

Referral criteria to hospital

- all large wounds need elective suturing
- suspected rabid animal bite
- shock and bleeding
- deep wounds.

Referral letter

Lone Street Pharmacy
12 Lone Street
Yeoville, 1234

Dear Colleague,

Alex, a 12-year-old boy, was brought to Lone Street Pharmacy by his father who wanted to buy dressings for a dog bite. In my opinion the wound needs to be sutured. The boy also needs prophylactic antibiotics and tetanus and rabies vaccination.

Please continue with care as seen appropriate.

Regards,

PJ Stuarts BPharm
Pharmacist

Down-referral

Many patients with chronic conditions require hospitalization or specialized care to stabilize their condition. Once the condition is stabilized and controlled for some time the patient does not require specialized care and may be managed and monitored in a less specialized and therefore less costly setting. The pharmacist needs to identify those patients that can be treated at a lower level.

ILLUSTRATIVE CASE STUDY – CASE STUDY 2.7

Mr A, a 67-year-old patient with severe uncontrolled hypertension (180/120 mmHg) has been admitted to a tertiary (teaching) hospital for blood pressure control. After a week his blood pressure was stable at 150/90 mmHg on hydrochlorothiazide, atenolol and enalapril. On discharge the patient received a prescription for the medicines mentioned above and was requested to come back monthly to the hypertension clinic at the hospital. After six months on the same therapy his blood pressure was still stable at 140/80 mmHg and he was doing very well with no other medical problems. However, the patient was complaining to the pharmacist that it cost him a substantial amount to come to the hospital every month and that he would like to receive his treatment from a primary health care clinic or pharmacy in his home town.

As part of the care plan the pharmacist has to ensure that the patient's condition is stable and under control by following Step 1 in the pharmaceutical care process prior to referral. Furthermore, the prescribed medicines must be available at the referral site and the patient must be referred to a specific person or clinic that will take over care. The patient should be informed where to go and whom to see at the clinic. It should also be clear to the patient and the health worker to whom the patient is referred, when the patient has to go back to the referral hospital.

The patient's blood pressure has been acceptable and stable for the past six months. A patient with a stable well-controlled blood pressure does not have to see the prescriber monthly for follow-up but could receive a repeat prescription or could be sent to a primary health care clinic for follow-up and to obtain the repeat prescription medicines at the clinic.

At the referral clinic the patient would need the monthly supply of his anti-hypertension medications and a contact person who should monitor his blood pressure periodically. It is important, however, that the patient's blood pressure be monitored regularly and not only that he receive the prescribed medication.

The following is an example of a referral letter for Mr A.

Referral letter

Dear Doctor/Pharmacist/Nurse

Following our telephone conversation this morning regarding the down-referral of Mr A.

Mr A, a 67-year-old, was admitted to Ga-Rankuwa Hospital with severe uncontrolled hypertension (180/120 mmHg) seven months ago. His blood pressure responded well on hydrochlorothiazide, atenolol and enalapril. Currently his hypertension is well controlled (140/80 mmHg) on these three antihypertensive agents. He has no other apparent medical problems. He received his prescription regularly for the past six months from the pharmacy at Ga-Rankuwa Hospital but the transport cost to the hospital is high and he requested to obtain his prescription at your clinic. Mr A is on hydrochlorothiazide 12.5 mg daily, atenolol 100 mg daily and enalapril 20 mg daily. We would like to see Mr A again in six months time at the hypertension clinic at Ga-Rankuwa Hospital. Please contact me or the hypertension clinic for any assistance regarding Mr A's therapy and to arrange a follow-up visit in six months time.

Signed: Pharmacist at Ga-Rankuwa Hospital

Social referral

Substance abuse and social habits could influence the patient's well-being and drug therapy. As part of the pharmaceutical care plan it may be necessary to refer the patient to a counsellor or institution.

ILLUSTRATIVE CASE STUDY – CASE STUDY 2.8

Mr X, a patient well-known to the pharmacy staff, comes in regularly to buy two bottles of a potential dependence-producing, scheduled cough mixture. Every time the pharmacist sells the cough mixture to the patient he explains the side-effects and the potential of getting addicted to the cough mixture. The pharmacist also advises Mr X that if his cough is not responding to the therapy he should see a doctor.

A while later the pharmacist discovers that Mr X has been purchasing the same cough mixture from other pharmacies and is abusing the mixture seriously. The pharmacist realises that the patient does not have the problem under control. Instead of confronting Mr X, the pharmacist increases his efforts to gain control. He informs his colleagues regarding Mr X's high usage of cough mixtures.

The pharmacist, being a family friend, is called for help when Mr X is charged for driving negligently while under the influence of alcohol and/or drugs. The pharmacist convinces Mr X to see a social worker or drug abuse counsellor.

Referral letter

Dear Colleague,

Following our telephone conversation regarding Mr X's referral.

Thank you for agreeing to see Mr X. Mr X, a patient well-known to the pharmacy staff, has been using a dependence-producing scheduled cough mixture for some time. The use has increased gradually and it is now at a stage at which it affects his normal functioning. After being charged for driving while under the influence of alcohol and/or drugs he agreed to see a social worker or drug abuse counsellor.

It would be appreciated if you could attend to Mr X.

Signed: Pharmacist

2.6 Summary

Pharmaceutical care is a prospective patient-centred practice with a focus on identifying, resolving and preventing drug therapy problems. This objective is achieved by a patient care process comprising four steps: assess the patient's drug therapy needs; develop a care plan to meet those needs; implement the care plan; and evaluate and review the care plan. Pharmacists require a high level of knowledge and skills to deliver pharmaceutical care and an organizational structure to facilitate its delivery. This structure must provide for the referral of patients who cannot be managed at a particular level of care to a different level, where optimal pharmaceutical care can be provided. Ultimately, as patients benefit from appropriate drug therapy, this will also have a beneficial impact on their families and the communities in which they live and work.

2.7 Further reading

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Acknowledgements

A significant amount of the information, definitions and descriptions in this chapter is based on the work of Cipolle, Strand and Morley as published in their 1998 text entitled, *Pharmaceutical Care Practice* (McGraw-Hill).

The four steps of the pharmaceutical care process have been extracted and amended, with permission, from a Scottish document published by the Clinical Resource and Audit Group (CRAG, 1999). Responsibility for any errors or omissions lies with the current authors.

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Information management and the use of evidence

3.1 Introduction

The fields of pharmacy and pharmacotherapy are areas of rapid change, with new techniques, new products and new information about old products constantly being introduced. All health care professionals, including pharmacists, are faced with the constant challenge of new information, which they are required to “filter”, assimilate and use to improve their practice. Medicines can be one of the most cost-effective interventions in health care systems in terms of alleviating pain, suffering and even preventing death. In addition, they can contribute to savings of limited health care resources. However, the marketing practices used by many pharmaceutical companies make it very difficult to identify real improvements in the field of pharmaceuticals. It is therefore essential for pharmacists to understand and be able to use the tools of **critical appraisal** and **cost-effectiveness analysis** as they evaluate the huge amount of information that reaches them. They should also share their critical appraisals with other health care professionals, notably prescribers. The techniques used have been incorporated in the emerging disciplines of evidence-based medicine/pharmacotherapy and pharmaco-economics.

Evidence-based medicine has been defined as:

“...the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”

(Sackett et al.)¹

Evidence-based medicine (EBM) attempts to move practice and prescribing away from a circumstantial and anecdotal approach to a reliance on the best possible evidence for the effectiveness of a medicine or procedure. What EBM aims to do is to integrate the best research evidence with clinical expertise and patient values. The process applied in assessing clinical evidence is termed “critical appraisal”. More recently, EBM has been extended beyond individual patient care to accommodate a wider societal perspective (Sackett et al.). For instance, it is now used in the compilation of treatment guidelines and medicine formularies.² Pharmacoeconomics is the discipline used when clinical/therapeutic alternatives are evaluated from an economic viewpoint.

In many cases, however, practitioners do not have access to “best evidence” because of the circumstances in which they practice. In such cases, an approach often used is to develop specific prescribing guidelines. In this way the number of choices is restricted to those which are expected to produce the best possible results, particularly in resource-limited environments. The relevant evidence is used to develop **standard treatment guidelines**, protocols or clinical guidelines to assist the process of decision-making and to contribute to rational and cost-effective health care.

This chapter aims to provide the pharmacist with information about ways to keep up to date with changes in information, legislation, training and outcomes methods. It also provides

an overview of drug information resources that are available in print and/or electronically and provides guidelines for interpreting and evaluating these and other information sources.

3.2 Main learning objective

- Describe and demonstrate the use of “best evidence” in pharmacy practice .
- Describe and demonstrate the use of pharmaco-economic analysis in pharmacy practice.

The underlying principle in these applications is that choice and follow-up action are taken **on the basis of the evidence** and from the perspective of the health care provider and the patient. The assumption is that the decision-maker is fully informed about the clinical and financial implications of each choice. Once the objective has been defined, the decision-maker/group should undertake a comprehensive evaluation and comparison of all possible options. This approach assumes that the decision-maker has unlimited time, knowledge and computational facilities. However, trade-offs between individual and societal “best interest” are also common.

Bounded rationality, which involves the construction of a manageable, simplified model of the real situation, has been suggested as an alternative approach.³ Decision-makers then adopt a rational approach to this model, based on their group’s point of view or perspective.

In either case, the objective is not only to identify the most suitable medicine in a particular situation, but also the one which is the most cost-effective. As stated above, **critical appraisal** is used to identify the best clinical / therapeutic alternative and pharmaco-economic analysis to identify that which is most cost-effective.

3.3 Continuing professional development (CPD) and life-long learning

Keeping up to date both scientifically and professionally is probably the most important demand throughout the career of a pharmacist. As the role of the pharmacist evolves and becomes more focused on pharmaceutical care, there is a need for greater involvement by the pharmacist in the outcome of drug therapy and the management of the individual patient’s medicines. The pharmacist is also facing new opportunities in all fields of pharmacy as well as an explosion in the amount of new medicine information that is available. If pharmacists are to stay abreast of changing demands, continuing professional development (CPD) is essential. Moreover, in many countries the regulatory body requires evidence not only that newly qualified pharmacists are competent to practice but also that they remain competent and fit to practice.

The development of antiretroviral therapy (ART) for AIDS is a good example of the massive increase in new medicines information and of the need for pharmacists to remain up to date. In 2001 there were 18 antiretroviral medicines for AIDS on the market and almost 100 investigational new medicine applications submitted to the U.S Food and Drug Administration to conduct clinical trials on patients with HIV or AIDS. Many of these and many other new medicines will be on the market within the next few years. Pharmacists need to keep up with information about these medicines to be able to make recommendations on their use and inclusion in formularies. Many health workers rely on textbooks,

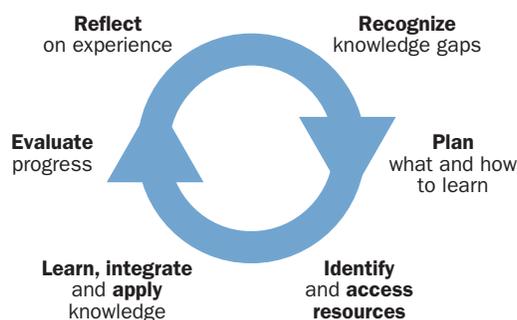
journals and educational meetings to keep themselves up to date. Improving professional practice so that the patient can receive better health care is an important aim of CPD. FIP defined CPD as *“the responsibility of individual pharmacists for systematic maintenance, development and broadening of knowledge, skills and attitudes, to ensure continuing competence as a professional throughout their careers.”*⁴

CPD is not the same as **continuing education** (CE) and is not an indication of the number of hours spent attending lectures or courses. It requires a positive attitude towards life-long learning and involves all learning activities that contribute to improving the competency and practice of a pharmacist.

Analysis of the literature indicates that while education through lectures alone is unlikely to change professional practice, intervention (interactive) workshops can lead to improvements.⁵

Since CPD focuses on the individual’s needs, each pharmacist has the responsibility to identify the needs in their own practice and identify a learning activity that will fulfil that need. Identification of individual needs is a continuous process, requiring an attitude of life-long learning. CPD is incorporated in the cycle of life-long learning.

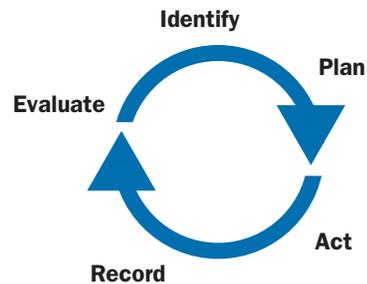
Figure 3.1 The cycle of life-long learning



ILLUSTRATIVE CASE STUDY – CASE 3.1

Cindy works in a community pharmacy. She previously worked in the production unit of a pharmaceutical company. She works with and helps to tutor one training pharmacist and two support personnel, both of whom are in the process of obtaining a formal qualification as pharmacist assistants. Cindy has a very good working relationship with the health care professionals in the area, who include a physiotherapist, two private doctors and nurses in the central community clinic. They often call on her to enquire about new medicines and drug-related problems, as do her patients, since they know that she always keeps up to date with new information. Cindy has developed the reputation of being a competent seven-star pharmacist in her area of practice. Cindy’s training pharmacist, who is already very competent, would like to develop the same reputation and would like to know how to achieve this. Cindy could use CPD to develop her professional practice.

CPD includes all learning activities that help to improve practice. The five key elements are identifying gaps (self-appraisal), personal planning, action (implementation), recording (documentation) and evaluation.

Figure 3.2 The CPD cycle**Self-appraisal**

It is important to reflect on our day-to-day experience and determine what can be learned from the experience or what development or need is necessary to make the experience more meaningful. These needs may be identified by personal assessment, performance review by a manager, audit exercise and professional requirements.

Planning

Since CPD is focused on individual professional needs, it is important to identify learning activities that are appropriate for the individual. In selecting learning activities it is important to consider the preferred learning style, time and resources.

Action

Participate in learning activities e.g., presentations, tutoring, meetings, workshops, teaching, talking with colleagues and experts, formal studies, self study and others.

Documentation

CPD requires the documentation of the different stages. This documentation, your portfolio, will serve as proof that you participated actively in developing your professional practice. CPD is a structured approach but incidental learning, the learning that takes place during daily activities, should not be ignored. It is important to document these. Documentation of all CPD activities should be kept and presented when required.

Evaluation

After completing a learning activity the success of the activity should be evaluated. The following questions could be asked:

- What can I do now that I could not do before?
- What do I know now that I did not know before?
- What is the impact of the learning activity on my practice? What further needs have been identified?

3.4 Critical appraisal in pharmacy practice**3.4.1 Sources of medicines information**

Numerous resources of medicines information are available, including reference books, drug compendia, national medicines lists, essential medicines and treatment guidelines, drug formularies, drug bulletins, medical journals, drug information centres, computerized information and the pharmaceutical industry.

Reference books

Numerous reference books exist on a wide range of topics. It is therefore important to evaluate the quality of each publication. The frequency of new editions is an important criterion in choosing reference books. Only publications that are revised every two to five years can provide up-to-date knowledge. Even then they are not fully up to date since considerable time is needed to complete the different phases of writing, editing and publishing the books.

Reference books that cover general pharmacology are Goodman and Gilman's *The Pharmacological Basis of Therapeutics* and *Clinical Pharmacology* by Laurence and Bennett. *Pharmacotherapy: A Pathophysiologic Approach* edited by DePiro et al. is an example of a text book on pharmacotherapy. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring* by Evans et al. provides information on pharmacokinetics and therapeutic drug monitoring. *Hansten and Horn's Drug Interactions Analysis and Management* is a primary source for information on drug interactions. In addition, Martindale's *The Complete Drug Reference* and the *AHFS Drug Information* provide detailed drug information on a wide range of medicines.

Drug compendia

Drug compendia vary in scope and content and are published in many countries. Compendia usually include generic and brand names, chemical composition, indications and contraindications, warnings, precautions and interactions, side-effects, administration and dosing guidelines. Some compendia like the *Physician's Desk Reference* in the USA are based on official labelling information for the product as proved by the regulatory authority. Others like the *Monthly Index of Medical Specialities (MIMS)* are commercially sponsored. The *United States Pharmacopeia Dispensing Information (USP DI)* and the *British National Formulary (BNF)* (<http://www.bnf.org/>) are comprehensive and objective compendia and provide information on comparative assessments, as well as criteria for choice within well-defined therapeutic categories.

National lists of essential medicines, treatment guidelines and drug formularies

National lists of essential medicines with or without standard treatment guidelines exist in many developing countries. These lists are based on consensus of what are the most common diseases and complaints and define the range of medicines that are available for a specific level of care. You should verify whether such treatment guidelines exist in your country and try to obtain the most recent edition. If no national list of essential medicines is available, the WHO Model List of Essential Medicines can be consulted instead. The WHO Model List, which is updated every two years, is available in print and at the WHO Essential Medicines Library, an electronic database that supports the selection of essential medicines. It includes data such as summaries of relevant WHO clinical guidelines, the most important systematic reviews, important references, indicative cost information, information on nomenclature, and quality assurance standards.

The *WHO Model Formulary 2004* presents model formulary information for all medicines on the WHO Model List of Essential Medicines and provides a starting point for countries wishing to develop their own national formularies. It is available in print, as a CD-ROM and at the following web site:

<http://mednet3.who.int/EMLib/>

National or institutional drug formularies are usually developed by therapeutic committees and contain the list of medicines that are approved for use in a specific institution, district, region or country. Many health insurance companies, hospitals, and care centres have their own formulary, listing the products that are reimbursed.

Drug bulletins

Drug bulletins can be a valuable source of information in keeping up to date. Many drug bulletins are not sponsored by the pharmaceutical industry and provide impartial assessment of medicines and practical recommendations based on comparison between treatment alternatives. Examples include the following.

- *Drug and Therapeutics Bulletin* (UK)
- *Medical Letter* (USA) (subscription only)
- *Therapeutics Letter* <http://www.ti.ubc.ca/pages/letter.html> (also available in Spanish)
- *Australian Prescriber* (Australia) <http://www.australianprescriber.com>
- *la revue Prescrire* <http://www.prescrire.com> (published in French)
- *Medscape* <http://www.medscape.com>

Journals

There is a wide range of journals available that can assist the pharmacist in keeping up to date in the different aspects of pharmaceutical practice. *Pharmacotherapy*, *The Annals of Pharmacotherapy* and *Expert Opinion on Pharmacotherapy* provide information on pharmacotherapy. The general medical journals such as the *Lancet*, the *New England Journal of Medicine* and the *British Medical Journal* provide information on patient care and pharmacotherapy. The *American Journal of Health-System Pharmacy* provides information on pharmacy in health systems and patient care. The *International Journal of Pharmacy Practice* is an example of a journal that focuses on pharmacy practice. Although good medical journals are peer-reviewed, do not assume that because a review article or researched study appears in print it is necessarily good science. Use the guidelines described in Section 3.4.2 below to evaluate all material.

Drug information centres

Before responding to any queries, the pharmacist should first ensure that the information obtained is reliable (see Section 3.4.4 below on how to evaluate the medical literature). Many countries have drug information centres and often these centres also provide information on poisons. For example, the UK Medicines Information Pharmacists Group provides medicines information on their web site at: <http://www.druginfozone.org/>

Elsewhere, the Pharmaceutical Clearing House and the Pan-American Pharmaceutical Forum, developed by the Pan American Health Organization (PAHO) and WHO, are also important references for obtaining drug information and for keeping up to date.

Other useful sites include the following:

WHO Essential Medicines Library: <http://mednet3.who.int/EMLib/>

Free Medical Journals site: <http://www.freemedicaljournals.com> which is dedicated to the promotion of free access to medical journals over the Internet.

Catalogue of Internet health resources with links to relevant sites: <http://www.bubl.ac.uk/link/med.html>.

TRIP was created to bring together all the 'evidence-based' health care resources available on the Internet. A basic version of the TRIP database can be searched without a subscription: <http://www.tripdatabase.com>

Micromedex is a subscription-based computer information package that provides information on medicines (DrugDex), diseases (DiseaseDex) and kinetics (KinetiDex): <http://www.micromedex.com>

LEARNING ACTIVITY 3.1

SoGood, a new medicine has just been registered in your country. A patient asks you for more information on the new product. Make a list of possible sources of drug information available to you. Which ones are more likely to be of use in answering this request?

3.4.2 How to retrieve (and evaluate) medicines information online

Many medical articles are indexed in the Medline database, which is available in most medical and science libraries. Medline is compiled by the National Library of Medicine of the United States and indexes over 3800 journals published in over 70 countries. Free access to the Medline database is available through the Internet by using the following Internet address: <http://www.ncbi.nlm.nih.gov/PubMed/>

Articles can be traced by using any word listed in the database as keywords. The words listed in the database include words in the title, abstract, authors' names and the institution where the research was done. Other sites such as <http://www.medscape.com/> or <http://biomail.sourceforge.net/biomail/> can also be used to search for information.

It is essential to ensure that the data obtained online are reliable. The following points can be used to determine if an article published on the Internet is authoritative:

- What is the author's qualification for writing on the subject?
- Is the author connected to an organization with an established reputation?
- Look for the source. Is it a major university or institute specializing in that area?
- Is it published on a reputable website? Has it been peer-reviewed?
- Has the author taken care in formatting, logic, structure and development of the argument?
- Does the article meet all the criteria as discussed in Section 3.4.4?

The following web site (also to be used in Learning Activity 3.4 below) is a useful source of criteria for evaluating content:

Grassian E. Thinking critically about world wide web resources. UCLA College Library. Available at: <http://www.library.ucla.edu/libraries/college/help/critical/index.htm>

LEARNING ACTIVITY 3.2

ACTIVITY A

Use an online database, such as PubMed, to find articles on pharmaceutical care.

ACTIVITY B

Narrow down your search to pharmaceutical care in ambulatory care.

3.4.3 How to obtain relevant information from a pharmaceutical representative (“drug rep”)

The pharmaceutical industry has large budgets for promotion and uses many different channels of communication for promoting products. However, commercial information often emphasizes only the positive aspects of the products. It is therefore important to take control of an appointment with a “drug rep” in order to obtain the less positive information as well. Because pharmacists are members of committees or groups that decide on a formulary or protocol, they are often subjected to promotional pressures by representatives. The pharmacist needs to be fully aware of the content of promotional materials in order to put forward a rational argument for the appropriate use of medicines.

LEARNING ACTIVITY 3.3

A representative from a pharmaceutical company has made an appointment to see you. The purpose of the meeting is to inform you about their new, very potent antibiotic. Use the guidelines shown below to conduct the meeting.

The following guidelines may be used to obtain the most out of a visit by a “drug rep”.

- See the “rep” only by appointment, determine the purpose of the visit in advance and confine the interview to that specific purpose.
- Take charge of the interview. Do not hear out a rehearsed sales routine but ask specific questions, especially about the adverse drug reactions and the therapeutic value of the product.
- Request independent published evidence from reputable peer-reviewed journals.
- Promotion brochures often contain unpublished material, misleading graphs and selective quotations. The pharmacist needs to appraise them so as to be able to deal with prescribers who have been influenced by the graphics and claims.
- Ignore anecdotal “evidence” such as the fact that a medical celebrity or major institution is prescribing or using the product.
- Request evidence by using the “STEP” analysis:
 - Safety** – the likelihood of long-term or serious side-effects caused by the product;
 - Tolerability** – is best measured by comparing the pooled withdrawal rates between the product and its most significant competitor;
 - Efficacy** – the most relevant dimension is how the product compares with your current favourite;
 - Price** – direct plus indirect costs should be taken into account.
- Ask for copies of papers of any clinical trials used to support the company’s argument. Evaluate the evidence stringently, paying particular attention to the power (sample size) and methodological quality of clinical trials and the use of surrogate end points. Do not accept theoretical arguments in the product’s favour without direct evidence that they translate into clinical benefit. Bear in mind that negative papers are unlikely to be quoted or referenced in the promotional literature or mentioned by the rep. Do an independent search of the literature.

- Do not accept the newness of a product as an argument for changing to it. There are good scientific arguments for doing the opposite. A new medicine is not always better or safer.
- Decline to try the product through starter packs or by participating in small-scale uncontrolled “research studies”.
- Record in writing the content of the interview and return to these notes if the rep requests another meeting with you.

(Greenhalgh, 1997)⁶

3.4.4 *How to evaluate the medical literature*

As the number of publications describing new treatment options in health care increases, the need to evaluate the medical literature critically becomes even more important. It is only after a critical review that a pharmacist can derive valid conclusions and incorporate the information into pharmaceutical care and practice.

The following three questions will help you.

- Why was the study done and what hypotheses were tested?
- What type of study was done?
- Was the study design appropriate for the purpose of the study?

Most papers have a similar format, which includes the introduction, methods, results and discussion.

- The **Introduction** should acquaint the reader with the problem statement and provide the necessary background to enable the reader to understand the problem and evaluate the outcome of the study. A well-defined study objective should also be stated in the Introduction.
- The **Methods** section should be clear and detailed enough so that the reader could repeat the investigation. The study design and sample should be clear to the reader. The statistical methods used should be stated in the Methods.
- A well-written **Results** section should present data on all subjects involved in the study and measured parameters as mentioned in the Methods.
- In the **Discussion**, the results are interpreted and related to, or compared with, previous work or practice. The reader should be aware of biased language and comments unjustified by the results. The reader should be aware that small differences in results may have been overemphasized by stating the differences in percentages. For example, if 5 out of 1000 patients experience an adverse effect on Medicine A and 10 out of 1000 on Medicine B the difference in experiencing adverse effects could be expressed as 50% more in Medicine B than Medicine A. In other words, the **relative risk reduction** (RRR) achieved using Medicine A rather than Medicine B is 50%, whereas the **absolute risk reduction** (ARR) is 0.5%. The calculation of absolute and relative risk reductions is shown in case study 3.2 below.

LEARNING ACTIVITY 3.4

Take one article on pharmaceutical care and evaluate the contents by using the points in 3.4.2 above and the criteria to be found on the web site indicated in 3.4.2.

The evidence-based approach turns clinical and economic problems into questions, followed by a systematic literature search and comprehensive analyses to inform decisions.

Table 3.1 Summary of basic criteria for critical appraisal of studies on therapy

Steps	Key factors
Validate study results	Randomization Follow-up Accountability of study participants Blinding (see Box 3.1 below)
Determine relevance of study results	Treatment effect
Determine applicability of study results	Patient's characteristics Feasibility of treatment as it relates to setting Benefits and harms Patient's preferences

(Correa-de-Araujo, 2001)⁷

The following questions assist the process of moving through these steps.

1. Does the medicine of interest have any therapeutic advantages over a currently used product?
2. Does the medicine of interest have any safety advantages over the currently used product?

If the answer to these questions is no, then the matter should not be pursued, and the current/comparator product should continue to be used. For the pharmacist in the patient care setting, the question would be asked in terms of verifying the decision made by the prescriber: is the medicine prescribed the best choice related to the indication?

The process of "systematic review" of the literature can be applied to answer these questions. Systematic review may be supported by a technique known as **meta-analysis** in some cases.

A **systematic review** is the process of systematically locating, appraising and synthesizing evidence from scientific studies in order to obtain a reliable overview. Systematic reviews are distinct from traditional literature reviews in that they are based on a strict scientific design to minimize bias and ensure reliability.⁸

Best evidence is based on selecting appropriate study types and evaluating the methodological quality of the studies.

BOX 3.1 TYPES OF STUDIES

In **retrospective** studies, historical data (i.e., data referring to past events) are collected e.g., from patient files or by interviews. In **prospective** studies, data are collected forward in time from the start of the study.

In **observational** studies, the researcher collects data from one or more groups of patients, but does not influence events. Observational studies may be prospective or retrospective. Observational studies include surveys, most epidemiological studies, and the study types described briefly below:

Case-control studies: retrospective comparison of two groups with and without a risk factor for a disease. Assignment to the risk factor group has to rely on memory or records, the selection of a comparable control group (i.e., risk factor-free group) is difficult, and confounding factors (i.e., factors whose effects cannot be separated from those of the factor being studied) may be present.

Cross-sectional studies are prospective studies conducted over a short period of time (“snapshots”). Confounding factors may be unequally distributed in the different groups, and group sizes may be unequal. This type of study can only establish that two factors are associated, not that one is the cause of the other.

Cohort studies consist of prospective observation of one or more groups with certain characteristics. The characteristic being studied may be linked to a hidden confounding factor.

In **experimental** studies the researcher performs an intervention, i.e., an experimental treatment, and assesses its effects. Experimental studies are always prospective. Experimental studies of medical treatments in humans are called clinical trials. In **uncontrolled** trials the experimental treatment is studied on its own, while in **controlled** trials it is compared with an alternative treatment or placebo, which allows the researcher to assess the relative effects of the treatments studied. In a **blinded** study, the participants do not know which treatment they are receiving; in a **double-blind** study, neither the participants nor the investigator know. In a **cross-over** design, participants serve as their own controls in that they are exposed to both treatments in turn. This design can only be used for treatments with non-permanent effects. An insufficient “washout” period in between can influence the outcomes. In a **randomized controlled trial** (RCT), participants are randomly assigned to the experimental groups. Randomization and blinding both contribute to minimizing bias.

A **meta-analysis** is “a statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be “combinable” usually to the level of re-analysing the original data, also sometimes called: pooling, quantitative synthesis”

(Huque, 1988).⁹

Guidelines for levels of evidence and the strength of recommendations from it have been developed. Amongst the best known are those of the Scottish Intercollegiate Guideline Network (SIGN).¹⁰

SIGN recommends that evidence for guideline development should be identified by systematic review and that guideline developers should state what search strategies and inclusion criteria were used to identify evidence. Where possible, formal meta-analysis should be quoted to synthesize results across studies. The definitions of the types of evidence and the grading of recommendations used by SIGN are set out in the Tables shown below.

Table 3.2 Levels of evidence

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

(Source: SIGN web site, 2003)

Table 3.3 Grading of recommendations

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

(SIGN web site)

The example of a **critical appraisal checklist** shown below illustrates the process of judging the validity of systematic reviews.

BOX 3.2 CRITICAL APPRAISAL CHECKLIST

Screening questions: On first reading, is there sufficient information to make a detailed appraisal? Is this a highly contentious review on a topic of clear importance to the health service? Is there no obvious alternative review of better quality available?

Has a clear **review question** been defined in terms of the question type, the population, intervention and outcome? Based on the question, can the review be executed systematically (**internal validity**) and does it achieve a good fit with the target question (**external validity**)?

Does the review state the types of **study designs** which were included and put them into the context of an appropriate hierarchy of evidence (see Box 2.1 above). Are inclusion/exclusion criteria for studies clearly stated? Are they consistent with the review question?

Is the **literature search strategy** recorded? Is it likely to have included most potentially relevant studies? Was the validity of included studies assessed? Was a sensitivity analysis performed to evaluate the effect of likely missing data? Were irrelevant studies excluded, and is there a list of excluded studies?

How were relevant **data abstracted**? Was this process consistent with the review question?

Were the following steps in the review **reproducible and bias-free**: Searching for all potentially relevant studies; applying study inclusion/exclusion criteria; assessing the validity of included studies; and abstracting data.

What is the **bottom line** as stated in the review? Is it relevant? Is it justifiable? What is the summary estimate of effect for each outcome examined? Was meta-analysis used, and if so, was it used appropriately in relation to the homogeneity or heterogeneity of the results; and the role of chance, as indicated e.g. by confidence intervals?

Is the review **up to date**? What were the cut-off dates for ascertainment of relevant literature?

What is the general quality of the review? Which elements might make it systematic? What are its potential uses?

(Adapted from: Aggressive Research Intelligence Facility of the University of Birmingham, UK)¹¹

See also 3.4.4 for information on how to evaluate the medical literature.

LEARNING ACTIVITY 3.5

Consider the systematic review by D. Wilkinson et al. entitled “Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomized placebo controlled trials” (see Appendix 1).

1. Use the checklist provided below to appraise the review.
2. At what level of evidence is this review?
3. What criticism do you have, if any, of systematic reviews and/or meta-analyses?

Clear review question stated (question type, population, intervention and outcome)?	
Included study designs stated?	
Criteria used to assess the quality of studies	(List:)
Study characteristics documented for included studies?	
Inclusion/exclusion criteria stated?	
Literature search strategy recorded?	
Data abstracted in a manner consistent with the review question?	
Reproducible and bias-free process of <ul style="list-style-type: none"> — identifying studies? — including studies? — abstracting data? 	
Relevant, justifiable bottom line ?	
Meta-analysis for different outcomes used (appropriately)?	
Up to date ?	

The Cochrane Collaboration

The most extensive system worldwide for the review of clinical trials is the Cochrane Database of Systematic Reviews. According to its own mission statement:

“The Cochrane Collaboration is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. It is a not-for-profit organisation, established as a company, limited by guarantee, and registered as a charity in the UK.”

(Cochrane Collaboration mission statement)

The activities of the Cochrane Collaboration and the resources made available are described on the Collaboration’s website (www.cochrane.org/cochrane/leaflet.htm).

Case study 3.2 provides an example of the way in which the Cochrane Library can be used to answer a treatment question is shown in the following example. We have used this example because of the major problem of the development of antimicrobial resistance and the need to always compare older medicines with heavily promoted newer ones.

ILLUSTRATIVE CASE STUDY – CASE 3. 2**ASYMPTOMATIC BACTERIURIA IN PREGNANCY**

(adapted from: *Therapeutics Letter*, issue 41, May/June/July 2001)

On 1st June 2001, you receive a phone call from a medical colleague about a 32-year-old woman who is three months pregnant. Your colleague wishes to prescribe an antibiotic for his patient whom he considers to have asymptomatic bacteriuria on the basis of an E. coli positive urine culture (>100,000 colonies/ml). He has told the patient that she should probably be treated with an antibiotic. When he suggested this approach, she said that she did not want to expose her foetus to any medicines unless it was absolutely necessary. In fact, she asked him “Why do I need to take an antibiotic anyway? What is the potential harm to my baby? And couldn’t I take cranberry juice, which I have heard is good for this problem?” He dissuaded her from the cranberry juice and wants to know which antibiotic would be best for her. You remember that at a recent CPD session the Cochrane Library www.cochrane.org was recommended as a reputable source of the best available evidence.(See reference 1 at the end of this case study.)

Evidence from the Cochrane Library

The most up-to-date information is available from the latest Cochrane Library CD-ROM. A less complete version is also available through OVID (UBC Library). When you do a search for bacteriuria using the CD-ROM, you get 14 hits in the Cochrane Database of Systematic Reviews, 9 complete reviews and 5 protocols (reviews in progress). When you double click on the reviews, you find 5 titles that are possibly relevant to this case: 1) Antibiotics for asymptomatic bacteriuria in pregnancy, 2) Duration of treatment for asymptomatic bacteriuria in pregnancy, 3) Treatment for symptomatic urinary tract infections during pregnancy, 4) Cranberries for treating urinary tract infections, and 5) Cranberries for preventing urinary tract infections. (See references 2-6.)

Double clicking on the first relevant review brings you to the abstract and full review. This review, updated on 28th December 2000, includes 14 randomized placebo controlled trials. The review concludes that antibiotic treatment is effective in clearing bacteriuria, reducing the incidence of pyelonephritis, and reducing the incidence of preterm delivery or low birth weight infants. The reviewer advises caution in interpreting the last outcome.

Quantitative evidence

Knowing that the patient may want some quantitative estimate of benefit, you need to look at the meta-analysis (quantitative summary of evidence). This can be done most quickly by clicking on “Find”, typing in “Metaview” and clicking on “Find Next”. Double clicking on the hypertext “Metaview, Tables and Figures” takes you to the meta-analysis figures. Double clicking on “Development of pyelonephritis” reveals that 13 trials included this outcome and that 9 of the 13 trials showed a significant reduction in pyelonephritis with antibiotics. The odds ratio (OR) is the summary statistic shown and is most useful when event rates are low. OR closely approximates the relative risk (RR) which is the better summary statistic in this case. (See reference 7.) An RR of 0.25 [0.19, 0.33] is found by clicking on “Statistic” and choosing “Relative Risk”. This means that the incidence of pyelonephritis is reduced by 75% (relative risk reduction) with antibiotic treatment. The bracketed numbers indicate the 95% confidence interval. This is narrow, demonstrating that the RR estimate is precise.

Clicking again on “Statistic” and on “Risk Difference” gives a summary statistic of - 0.146. Multiplying this number by 100 gives you an absolute risk reduction (ARR) of 14.6%. From this result, it is possible to calculate the number needed to treat by taking $100/ARR = 7$. This means that seven women with asymptomatic bacteriuria during pregnancy need to be treated with an antibiotic to prevent one case of pyelonephritis (see Table below).

Effect of antibiotics on the incidence of pyelonephritis (2)

Pyelonephritis (%)

Antibiotic	Untreated	RR	RRR (%)	ARR (%)	NNT
5	19	0.25	75	14.6	7

RR=relative risk; RRR=relative risk reduction; ARR=absolute risk reduction; NNT=number needed to treat to prevent one event.

NB: For a more detailed example of how to calculate the above parameters, see the pharmacoeconomic analysis shown in Appendix 2.

The rest of the meta-analysis shows that short-course antibiotic therapy (3–7 days) has similar effectiveness to continuous antibiotics until the end of pregnancy. The review highlights the fact that none of the included studies document the adverse effects of the antibiotics. A reassuring fact is that one potential adverse consequence, low birth weight or prematurity, was less in the antibiotic treated group.

You are now running short of time so you quickly double-click on the other four reviews. You learn from the abstract of the Duration of treatment for asymptomatic bacteriuria review (Jan. 2000) that there is insufficient evidence to conclude whether single dose antibiotic therapy is as good as 4–7 days of antibiotic therapy. (See reference 3). From the Treatment of symptomatic UTI abstract (Mar 2000), you learn there are insufficient data to recommend any one specific antibiotic regimen. (4) The Cranberries for treatment of UTI abstract (Aug. 1998) indicates that no randomized controlled trials met their inclusion criteria (scanning the review's text, you note that asymptomatic bacteriuria was included). (See reference 5). The Cranberries for prevention of UTI abstract (Aug. 1998) states that "The small number of poor quality trials gives no reliable evidence of the effectiveness of cranberry juice and other cranberry products". (See reference 6).

You then check the Motherisk website, a source of evidence-based information on the potential risks of therapeutic medicines during pregnancy (www.motherisk.org). This source confirms that penicillins are considered to have a wide margin of safety during pregnancy. You can now provide some evidence-based information to your colleague.

When the patient comes in for her prescription, you tell her that you would not recommend taking cranberry juice, as evidence for its effectiveness is lacking. You also tell her there is good evidence that a short course of antibiotics reduces the incidence of an infection of the kidneys during pregnancy. For every seven women like her who take a course of antibiotics, one case of kidney infection is prevented. After checking for a history of allergy to penicillins, you check that the recommended course of amoxicillin 500 mg TID for seven days has been prescribed, which is stated to be safe on the Motherisk web site. The patient can then choose whether or not to take the antibiotic.

Asymptomatic bacteriuria in perspective

The evidence in this case provides an answer for a woman with a positive culture, but does not answer the question whether all pregnant women should be screened. Asymptomatic bacteriuria occurs in about 6% of pregnant women. (See reference 8). Given a 14.6% ARR with an antibiotic (See reference 2), $1/(0.06 \times 0.146) = 114$ women would have to be screened to prevent one case of pyelonephritis.

Conclusions

Reliable sources of best available evidence are an aid to practice.

The Cochrane Library is a recognizably incomplete but expanding source of best available evidence.

Familiarity with the Cochrane Database of Systematic Reviews is necessary in order to be able to extract information effectively and efficiently.

References used in this example

1. Therapeutics initiative. Sources of drug therapy information. *Therapeutics Letter* 35 (May/June 2000).
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3.5 Pharmacoeconomic analysis

There are four main criteria to be considered in the selection and use of a medicine. They are efficacy, safety, quality and economic evaluation. “Value for money” is one of the underlying principles of pharmacoeconomic analysis.

Health economics is about making decisions on the most efficient use of limited resources for health care. Health managers must constantly decide which of several courses of action to follow in order to use their limited budgets to the greatest possible benefit. These may be choices among programmes, programme goals/objectives, or strategies or activities for achieving specific goals. These decisions are made at central level (e.g., How much should the public sector spend for all recurrent budgets? How much should be allocated to the different ministries?), at national departments of health (e.g., How much should be allocated to different programme activities? How much should be spent on medicines, personnel and other operating costs?), at local level (e.g., How much should be spent on medicines, training and storage? Which distribution strategy will deliver medicines to health facilities most efficiently? Which medicines should be purchased and used?), regional offices, district offices and individual facilities.

Economic evaluation comprises a set of analytical tools that can help identify which of several alternatives offers the greatest benefit compared with its cost.

Four methods of economic analysis are commonly used and are described here in increasing order of methodological and practical difficulty.

- **Cost-minimization analysis** calculates the cost of two or more alternatives that have the same outcome to identify the lowest-cost option.
- **Cost-effectiveness analysis** measures both costs and benefits of alternatives to find the strategy with the best ratio of benefits, measured in therapeutic or programme effects, per money unit.

- **Cost-utility analysis** measures the effect of interventions in both quantitative and qualitative terms, using utility-based units such as quality-adjusted life-years (QALYs).
- **Cost-benefit analysis** compares the costs and benefits of an intervention by translating the health benefits into a money value, so that both costs and benefits are measured in the same units. Cost-benefit analysis enables us to determine:
 1. whether an individual intervention provides a net overall gain, and
 2. how the gain from that intervention compares with the gain from other possible interventions.

There are six steps involved in the performance of an economic evaluation.

Table 3.4 Six-step economic evaluation

Step	Example
1. Define the objective	Prevent mother-to-child transmission (MTCT) of HIV
2. List the different ways to achieve the objective	A: Give nevirapine to mother and baby B: Perform no intervention
3. Identify and measure the costs of each option	<i>Costs of option A:</i> Introduction / monitoring / counselling Provision of nevirapine to all HIV+ pregnant women Treatment costs of infected infants <i>Costs of option B:</i> Treatment of infected infants
4. Identify and measure the benefits of each option	<i>Benefits of option A:</i> MTCT reduced from 32% to 16%: Costs for treatment of infected infants are halved For every 1000 births, 160 lives are saved <i>Benefits of option B:</i> No costs for introduction / monitoring / counselling or for providing nevirapine to all HIV-positive mothers
5. Calculate and interpret the cost-effectiveness of each option	Compare the costs and the benefits: Taking into account costs of counselling and nevirapine alone, option A is more expensive, but saves lives. You could calculate a cost per life saved When taking into account subsequent treatment costs of infected infants, option A is less expensive, and saves lives. The “cost” per life saved, or incremental cost-effectiveness ratio, would be negative
6. Perform sensitivity analysis on the conclusions	Consider possible variations: percentage of pregnant women reached, morbidity in treated mothers and/or infants etc.

Sensitivity analysis is a way to deal with uncertainties in assumptions underlying the economic analysis. It creates different scenarios. It includes the following steps:

- Identify the assumptions which are uncertain
- Determine their likely range
- Recalculate study results using the most conservative estimate, the “best guess” and the least conservative estimate.

How will the differences affect the conclusions?

In summary, pharmacoeconomic analysis allows decision-makers to choose from among alternative therapies, interventions and programmes by establishing the differences among them in quantitative (monetary) or qualitative (utility) terms. A cost-effectiveness ratio is calculated to compare the effectiveness of two medicines. The ratio is basically the result of dividing the difference in cost of the two interventions by their difference in benefits.

Calculated cost-effectiveness ratios may vary, depending on what costs and what outcomes (endpoints) are included in the analysis. Other than medicine costs, costs of monitoring or treating adverse effects could be considered. Savings can be achieved with cost offsets. On the other hand, a medicine which reduces the rate of an uncommon adverse effect is not likely to be cost-effective if the drug costs themselves are high.

The comparison of cost-effectiveness ratios is a way to determine the benefit achieved with an amount spent, i.e., to see whether a medicine represents value for money. Not all new medicines prove to be more cost-effective than existing ones. Cost-effectiveness in different settings, based on relevant outcomes, can only be demonstrated on the basis of data collected in high quality trials.

Note: Further information on pharmacoeconomic analysis may be obtained from the WHO manual Drug and Therapeutics Committees: A Practical Guide (2004).¹² An example from this manual is presented in Appendix 2.

LEARNING ACTIVITY 3.6

Based on the following data,¹³ compare the cost-effectiveness ratios of the universal use of nevirapine in pregnant women versus a targeted approach (i.e., using nevirapine in HIV-positive pregnancies only) for the prevention of MTCT of HIV/AIDS in a high prevalence setting.

- Hypothetical cohort of 1000 pregnant women in one year
- 30% seroprevalence of HIV
- Cost of screening and counselling: US\$6 per pregnant woman. Assume that screening misses 20% of those pregnant women who carry the HIV virus
- Risk of transmission of HIV with nevirapine: 160 in 1000 HIV+ pregnancies
- Risk of transmission of HIV with other short-course regimens: 260 in 1000 HIV+ pregnancies
- Hence: risk reduction with nevirapine regimen compared to other short-course regimens: 100 in 1000 HIV+ pregnancies = 10%
- Cost of nevirapine regimen per birth: US\$4

How many infections of infants can be averted with either programme? What is the cost of averting one infection for each programme? What is the difference of costs per infection averted? Use the table provided below to record the results of your calculations.

	Universal programme	Targeted programme
Number of pregnant women in the hypothetical cohort		
Number of HIV-positive pregnant women treated		
Cost of programme for the hypothetical cohort (treating all pregnant women, or screening all pregnant women and treating those found HIV-positive)		
Benefit: Number of infections averted in the hypothetical cohort		
Cost/benefit ratio: Cost per infection averted		
Incremental cost/benefit ratio: Difference (per infection averted) (Note that the benefit of the targeted approach achieved by avoiding adverse events with nevirapine in healthy pregnant women has not been included in this calculation).		

3.6 Using evidence to develop standard treatment guidelines and an essential medicines list (EML)

In most countries, the selection of medicines is a two-step process. The first step concerns market approval for a pharmaceutical product. Approval is usually granted on the basis of efficacy, safety and quality, and rarely on the basis of a comparison with other products already on the market or cost. This regulatory approval allows a product to be marketed in a country. In addition to the regulatory decision, many medicine procurement and insurance schemes have mechanisms to limit procurement and/or reimbursements of medicine costs. For these decisions a second selection step is needed, based on a comparison between various drug therapies and on considerations of value for money. The identification of a limited number of cost-effective “essential medicines” can help optimize the use of limited pharmaceutical budgets, especially in resource-poor settings.

Since 1977, WHO’s Model List of Essential Drugs¹⁴ has been updated regularly and has provided guidance for developing national and institutional essential medicines lists. According to WHO:¹⁵

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

The affordability concept was introduced into the description in 1999. By the end of that year, 156 WHO Member States had an official national essential medicines list, of which 127 had been updated in the last five years. Many national lists are linked to clinical guidelines and used for training and supervision, and to indicate the public health priorities for the pharmaceutical system. Although originally intended for developing countries, an increasing number of developed countries also use key components of the essential medicines concept. Examples are the positive reimbursement list of the Pharmaceutical Benefits Scheme of Australia, the Scottish Intercollegiate Guidelines Network (SIGN) clinical guidelines, and some health maintenance organizations in the USA. In most cases, this development was triggered by increasing medicine costs in general, and by the introduction of many new and often expensive medicines.

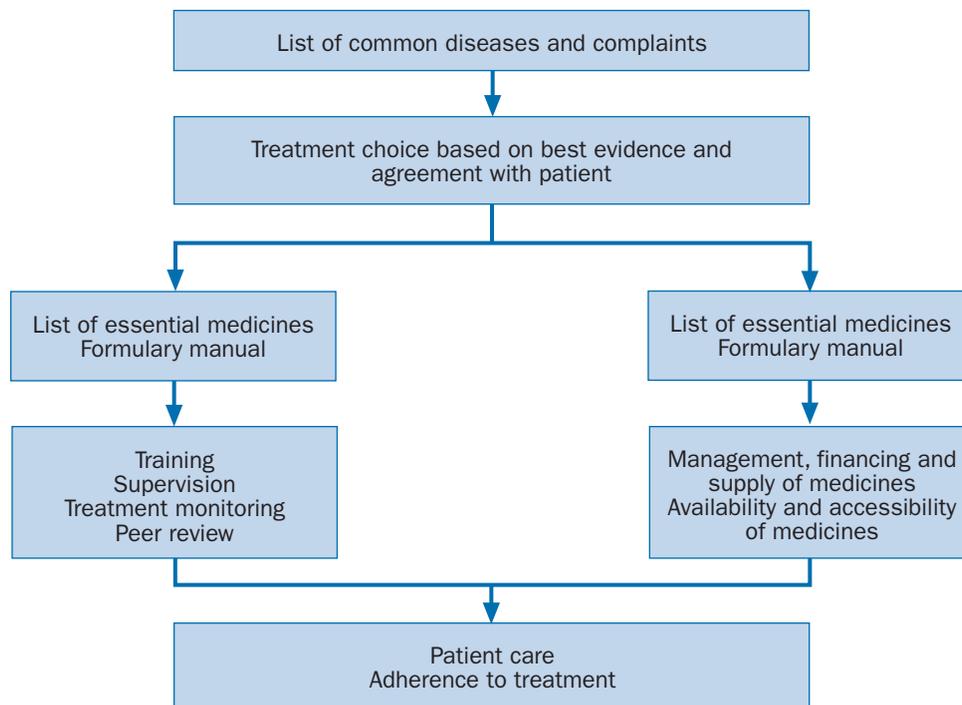
There are primary and secondary criteria for the selection of essential medicines. These criteria have changed slightly over the years. Currently, the primary selection criteria are: sound and adequate data of efficacy and safety from clinical studies; evidence of performance in different health care settings; availability in a form in which quality, including adequate bioavailability, can be assured; stability under the anticipated conditions of storage and use; total cost of the treatment; and single compounds. Where medicines appear to be similar in the above respects, comparative pharmacokinetic properties, and availability of facilities for manufacture or storage are used as secondary criteria.

A number of major trends have an impact on the use of essential medicines lists and procedures for updating and disseminating them. For example, many developed countries have embarked on large-scale programmes to develop evidence-based standard clinical guidelines. The science of evidence-based decision-making has rapidly become the international norm. Increasingly, the strength of recommendations is being linked to the strength of the underlying evidence.

While the early institutional essential medicines lists were supply lists drawn up by national drug procurement agencies, today decisions on national essential medicines lists are no longer taken in isolation and are increasingly subject to national clinical choices.

The techniques of critical appraisal and pharmacoeconomics outlined above are now used to identify the most appropriate treatment modality for a particular condition under the prevailing circumstances. The medicines required in this modality then go forward to become part of the essential medicines list. The overall process and the role of treatment guidelines and drug lists in improving health care are shown in Figure 3.3. below.

Figure 3.3 List of common diseases and complaints



Although this approach is important in contributing to rational, effective and cost-effective medicines supply and use, there are circumstances in which other measures may be necessary. For example, patented medicines are required where no generics are available for the prevention and treatment of conditions such as tuberculosis, malaria, HIV/AIDS and other public health priorities. Although relatively few patented medicines are currently included in the WHO Model List of Essential Medicines (e.g., fluconazole, nevirapine, praziquantel, spectinomycin, zidovudine) the number is likely to increase in the near future. These new treatments may be cost-effective (especially since there are few alternatives), but they are not necessarily affordable for the individual patient or for the community. The treatment of multidrug-resistant tuberculosis, for example, is about 20-30 times as expensive as the usual six-month DOTS regimen used for uncomplicated, non-resistant tuberculosis. In many countries, this creates a situation of competing demands on scarce health care resources. The major furore over the prices of antiretroviral medicines in developing countries illustrates this problem. Strategies such as market segmentation and differential pricing are currently being explored as a means to protect both patent-owners' rights and patients' right to health care, including essential medicines.

3.7 Limitations of and misperceptions about evidence-based practice

Evidence-based practice has a number of limitations. These include the shortage of accurate and reliable scientific evidence and the difficulties in applying what evidence is available to patient care within a specific system. Other important limitations include the need to develop new skills in searching and critically analysing the literature, the time health care professionals need to absorb and apply these new skills, and the effort and costs involved in making resources on evidence-based practice available at the point of care.

Meanwhile, there are a number of misperceptions about evidence-based practice – especially in relation to its impact on overall health care costs. Although an evidence-based approach can contribute to cost-containment by selecting and utilizing the most cost-effective options, it may also lead to the adoption of more expensive treatment modalities. This may occur because it is aimed at improving health care and hence the quality and quantity of life. As a result, the strict application of this principle may lead to the development and introduction of policies that result in increased costs.¹⁶

3.8 The patient's viewpoint

Throughout this discussion on the use of evidence in improving health care, the viewpoint of the patient has not been mentioned. However, the beliefs, values, preferences, concerns and economic situation of patients have a direct effect on their perceptions of the possible benefits and harms of, their acceptance of, and their adherence to specific treatment modalities and/or drug regimens. As shown in Table 3.1, considering the applicability to an individual patient is always the final step in the appraisal of evidence for therapy. The patient's characteristics, the feasibility of treatment as it relates to setting, benefits and harms, and the patient's own preferences all need to be taken into account. The selected strategy should be agreed with the patient; this agreement on outcome, and how it may be achieved, is termed **concordance**. Concordance is an important factor for adherence to therapy.

As far as patient-related factors for adherence are concerned, women tend to be more adherent than men, younger patients and the very elderly are less adherent, and people living alone are less adherent than those with partners or spouses. Specific education interventions have been shown to improve adherence. Patient characteristics such as illiteracy, poor eyesight or cultural attitudes (for example preference for traditional or alternative medicines and suspicion of modern medicine) may be very important in some individuals or societies. Such attitudes need to be discussed and brought out into the open.¹⁷ Other factors which influence adherence may be linked to the practitioner and his/her relationship with the patient, the health condition, the prescription, the dispenser or the health system. A good patient-practitioner relationship is crucial to concordance. "Satisfaction with the interview" on the part of the patient has been consistently shown to be one of the highest predictors of good adherence. Conditions with a severe prognosis (e.g., cancer) or painful conditions (e.g., rheumatoid arthritis) elicit better adherence rates than asymptomatic, "perceived as benign" conditions such as hypertension, or conditions which occur at long intervals, such as epilepsy. Prescriptions for many medications or for more than two doses per day tend to decrease adherence, as do adverse effects, which patients may not always mention. The dispenser's personality and professional manner is important, especially when generic medicines are substituted for brand name medicines.

The health care system may be the biggest hindrance of all to adherence. Long waiting times, uncaring staff, uncomfortable environments, exhausted drug supplies and long distances between the patient and the health care facility can all have a major impact on adherence.¹⁷

In some countries, Patient Charters have been established to accommodate patients' rights. These charters have certain common features concerning the ways in which patients should be treated, in particular:

- To be treated with dignity
- To be seen by a pharmacist who can be identified by name
- To be assured of confidentiality about their illness and treatment
- To receive pharmaceutical services in a pharmacy which complies with good pharmacy practice standards
- To expect the highest degree of honesty from their pharmacist in dealing with their medical funding
- To be advised and counselled on the appropriate use of medicines
- To receive the right medicine in the right quantity
- To receive safe, quality and effective medicines
- To feel able to complain or express a need
- To participate in decision-making on matters affecting their health and their medicine
- To get a second opinion.

At the same time, patients also have responsibilities:

- To be reasonable and courteous
- To assist their pharmacist in complying with legal requirements relating to medicine
- To use medicine with care
- To report any problems experienced with their medicine.

It is essential that patients are informed about their options when faced with dealing with their illness. These options can be clarified by the responses to a small number of questions.

Table 3.5 Treatment options for patients

Questions:	Example: Prophylaxis for malaria	
1. What will happen if I do nothing about my current complaint? 	I may contract malaria (Malaria is problematic, especially for pregnant women, children under 5 years and immunocompromised persons)	
2. What intervention options are available/feasible? 	Chemoprophylaxis — Non-drug prophylaxis (protective clothing, mosquito net, insect repellent, stay in rooms with air-conditioning or screens or treated with insecticide from dusk to dawn) — Stay away from malaria area	
3. What are the benefits and harms of the possible interventions? (What? When? How long-lasting? How probable?) 	— Chemoprophylaxis: efficient in preventing malaria if the correct medicines are used, but can have many side-effects — Non-drug prophylaxis: less effective in preventing malaria, can be inconvenient — Staying away from the area may be impossible	
4. What significance do the benefits and harms have for me? (How important are they to you? What are your preferences?) 	— Is the malaria area a high-risk area? — Will I stay there for a long time? If so, the risk increases, side-effects of chemoprophylaxis may be unacceptable in the long term — How efficiently will I be able to implement non-drug measures? — Will I have ready access to treatment if I do contract malaria?	
5. Do I have enough information to make a choice? (Do you have sufficient information on your current options? Is your range of options wide enough?) 	 NO – Obtain the necessary information and recycle through the flow chart (ask practitioner or get information elsewhere)	 YES – Implement best option

Adapted from: Irwig et al, 1999¹⁸

LEARNING ACTIVITY 3.7

Complete the table on the following page by giving responses for a patient who is HIV-positive and is at risk of contracting *Pneumocystis carinii pneumonia* (PCP).

Questions:		Response:
1. What will happen if I do nothing about my current complaint? ↓		
2. What intervention options are available/feasible? ↓		
3. What are the benefits and harms of the possible interventions? (What? When? How long-lasting? How probable?) ↓		
4. What significance do the benefits and harms have for me? (How important are they to you? What are your preferences?) ↓		
5. Do I have enough information to make a choice?		
↓ NO – Obtain the necessary information and recycle through the flow chart (ask practitioner or get information elsewhere).	↓ YES – Implement best option.	

3.9 Summary

In view of the constantly expanding choice of medicines on the pharmaceutical market, pharmacists need to keep up to date with information and new developments in order to help patients make informed treatment choices. Being able to rely on the best possible evidence for the effectiveness of a medicine or procedure is a major advantage. Best evidence is derived from identifying good quality clinical trials and synthesizing their results in order to gain a reliable overview. Well-known sources of evidence in the form of systematic reviews and meta-analyses include the Cochrane Library (<http://www.cochrane.org>) and the British Medical Journal's periodic publication *Clinical Evidence* (<http://www.clinicalevidence.com>).

Pharmacoeconomic analysis is used to identify the most cost-effective interventions. It can be used to relate the differences in costs between two treatments to their differences in benefits for a hypothetical group of patients treated (e.g., 1000 patients) to identify the treatment with the greatest benefits, given the frequency with which beneficial and adverse events have been reported in the literature.

Where clinical evidence and pharmacoeconomic analysis cannot be consulted directly, standard treatment guidelines or clinical guidelines based on these criteria may be used to assist decision-making between alternative treatments.

Although clinical evidence and pharmacoeconomic analysis can provide a basis for the selection of an effective and cost-effective treatment, the final decision must be based on the applicability of the treatment to the individual patient in terms of the patient's characteristics, the feasibility of treatment in the individual setting, expected benefits and harms, and the patient's preferences.

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Glossary

Absolute risk (AR): the probability that an individual will experience the specified outcome during a specified period. It lies in the range 0 to 1, or 0% to 100%. In contrast to common usage, the word **risk** may refer to adverse events (such as myocardial infarction), or desirable events (such as cure).

Absolute risk reduction (ARR): the absolute difference in risk between the experimental and control groups in a trial. It is used when the risk in the control group exceeds the risk in the experimental group, and is calculated by subtracting the AR in the experimental group from the AR in the control group. This figure does not give any ideas of the proportional reduction between the two groups. For this purpose, relative risk reduction (RRR) is needed (see below). For example, if 9 out of 45 persons in the control group and 6 out of 60 persons in the experimental group experience an adverse outcome, the absolute risk reduction would be $9/45 - 6/60 = 0.2 - 0.1 = 0.1$.

Adherence: the ability of a patient to adhere to a therapeutic regimen agreed upon between patient and practitioner (see concordance).

Antimicrobial resistance: the ability of micro-organisms to continue multiplying in the presence of therapeutic concentrations of the antimicrobial drug, thereby resulting in possible treatment failure. The minimum inhibitory concentration (needed to kill microbes) is higher than the concentrations achieved with therapeutic treatment.

Bias: systematic deviation of study results from the true results, due to the way(s) in which the study is conducted.

Bioavailability: the rate and extent to which a medicine or other substance becomes available to the target tissue after administration.

Blinding: a measure taken in experimental design to avoid bias, consisting in not disclosing which subjects in a study are allocated to which procedure (treatment). If both the experimenter and the subjects are unaware of the treatment allocation, the study is double-blind.

Care plan: a detailed schedule outlining the pharmacist's and the patient's activities and responsibilities, completed by the pharmacist, with the input and participation of the patient, designed to 1) resolve any drug therapy problems, 2) successfully achieve the therapeutic goals of the patient and prescriber; and 3) prevent any potential drug therapy problems.

Cognitive services (functions): those services or functions which require professional knowledge and skills beyond the ones required for the dispensing of a prescription medication, e.g. counselling, drug information, blood pressure monitoring, etc.

Compliance: the ability of a patient to comply with a therapeutic regimen prescribed by a practitioner. Patient compliance follows an authoritative therapeutic decision made by the practitioner rather than a shared decision-making process (see Adherence and Concordance).

Compounding: the preparation, mixing, assembling, packaging, or labelling of a medicine. Such a medicine is then dispensed to a patient on prescription or on initiative in the course of professional practice, by a pharmacist or prescriber. Alternatively, it can be used in research, for teaching, or for chemical analysis. Compounding is not manufacturing in the legal sense.

Concordance: shared decision making and agreement between the patient and the practitioner on the selected therapeutic strategy, its outcome, and how it may be achieved.

Confidence interval (CI): the 95% confidence interval (or 95% confidence limits) would include 95% of results from studies of the same size and design. This is close to but not identical to saying that the true size of the effect (never exactly known) has a 95% chance of falling within the confidence interval. If a confidence interval does not overlap the value against which the outcome should be judged (either a reference value or a limit of possible outcomes such as 0 or 100%), the result is considered to be significant.

Continuing professional development (CPD): the responsibility of individual pharmacists for systematic maintenance, development and broadening of knowledge, skills and attitudes, to ensure continuing competence as a professional throughout their careers.

Controls: in a randomized controlled trial, the participants in its comparison group. They are allocated either to placebo, or no treatment, or to the standard treatment.

Cost-benefit analysis compares the costs and benefits of an intervention by translating the health benefits into a money value, so that both costs and benefits are measured in the same units.

Cost-effectiveness analysis measures both costs and benefits of alternatives to find the strategy with the best ratio of benefits, measured in therapeutic or programme effects, per money unit.

Cost-minimization analysis calculates the cost of two or more alternatives that have the same outcome to identify the lowest-cost option.

Cost-utility analysis measures the effect of interventions in both quantitative and qualitative terms, using utility-based units such as quality-adjusted life-years (QALYs).

Critical appraisal: the process applied in assessing clinical evidence, used to identify the best clinical/therapeutic alternative.

Dispensing: interpretation and evaluation of a prescription, selection and manipulation or compounding of a pharmaceutical product, labelling and supply of the product in an appropriate container according to legal and regulatory requirements, and the provision of information and instructions by a pharmacist, or under the supervision of a pharmacist, to ensure the safe and effective use by the patient.

Distribution: activities required to receive pharmaceutical products from the supplier and to move them safely, securely and expeditiously to the points in the health care system where the products will be dispensed to the patients.

Drug therapy problem: an undesirable event, a patient experience that involves, or is suspected to involve drug therapy, and that actually or potentially interferes with a desired patient outcome.

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

Evidence-based medicine (EBM): the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

Health promotion: the process of enabling people to increase control over, and to improve, their health.

Incidence: a measure of morbidity based on the number of new episodes of illness arising in a population over an estimated period (as opposed to **prevalence:** a measure of morbidity based on current sickness in a population estimated at a particular time).

Managed care: system of health care delivery that influences utilisation and cost of services and measures performance with the objective to coordinate health care services in order to maximize benefits and minimize costs.

Meta-analysis: a statistical technique that summarizes the results of several studies in a single weighted estimate, in which more weight is given to results from higher quality studies.

Morbidity: rate of illness but not death.

Mortality: rate of death.

Noncommunicable disease: any disease that can NOT be transmitted from one person to another by direct physical contact, by common handling of an object that has picked up infective micro-organisms, through a disease carrier, or by spread of infected droplets coughed or exhaled into the air.

Number needed to treat (NNT): one measure of treatment effectiveness. It is the number of people you would need to treat with a specific intervention for a given period of time to prevent one additional adverse outcome or achieve one additional beneficial outcome. NNT can be calculated as $1/ARR$. For example, with an absolute risk reduction of 0.1 (see example under ARR), the NNT would be $1/0.1 = 10$ which means that 10 patients would need to be treated in order to prevent one adverse outcome.

Odds ratio (OR): one measure of treatment effectiveness. It is the odds of an event happening in the experimental group, expressed as a proportion of the odds of an event happening in the control group. The closer the OR is to one, the smaller the difference in effect between the experimental intervention and the control intervention. If the OR is greater (or less) than one, then the effects of the treatment are more (or less) than those of the control treatment. Note that the effects being measured may be adverse (e.g. death or disability) or desirable (e.g. survival). The OR is analogous to the relative risk (RR). Experimental designs which give rise to odds ratios include studies where the sample sizes of the different groups are not pre-determined, e.g. case-control studies. Odds ratios are also used to combine the results of different studies, because the odds can be calculated within the experimental group, independently of the comparative size of the control group, with is different in different studies.

Odds: the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.

Outcomes: consequences (results) of interventions made to meet therapeutic goals. Outcomes can have economic, social/behavioural or physiological characteristics.

P value: the probability that an observed difference occurred by chance if it is assumed that there is in fact no underlying difference between the means of the observations. If this probability is less than 1 in 20 (which is when the P value is less than 0.05), then the result is conventionally regarded as being 'statistically significant' (see below)

Pharmaceutical care: the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. It is a collaborative process that aims to prevent or identify and solve medicinal product and health-related problems. This is a continuous quality improvement process for the use of medicinal products.

Pharmaceutical practice includes the provision of pharmaceutical products, pharmaceutical services and pharmaceutical care and covers all those activities and services provided by pharmacists in the health care system.

Pharmaceutical services: all the services rendered by pharmaceutical staff to support the provision of pharmaceutical care. Beyond the supply of pharmaceutical products, pharmaceutical services include information, education and communication to promote public health, the provision of drug information and counselling, regulatory services, education and training of staff.

Pharmacist: a person professionally qualified in pharmacy, the branch of health sciences dealing with the preparation, dispensing and use of medicines. The role of the pharmacist has evolved from that of a provider of medicines to that of a provider of patient-centred pharmaceutical care.

Pharmacotherapy: treatment of health conditions with medicines.

Pharmacovigilance: defined by WHO as the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Pharmacy practice: the provision of medications and other health care products and services and to help people and society to make the best use of them.

Placebo: a biologically inert treatment given e.g. to the control group participants in a clinical trial.

Practitioner: a person who is professionally qualified to practice the delivery of health care services.

Prevalence: a measure of morbidity based on current sickness in a population estimated at a particular time (as opposed to incidence: a measure of morbidity based on the number of new episodes of illness arising in a population over an estimated period)

Prevention (preventive measures): measures which aim to thwart or ward off illness or disease prophylactically.

Procurement: the process of acquiring supplies from private or public suppliers or through purchases from manufacturers, distributors or agencies in order to ensure the availability of the correct medicines in the correct quantities at the lowest possible prices and at recognized standards of quality.

Qualitative data: data which describe underlying causes and reasons for a phenomenon in the form of non-categorized responses, e.g. responses to open-ended questions in interviews or discussions, as opposed to quantitative data, which describe the extent of a phenomenon in numerical terms.

Quality assurance (QA): technical, operational and managerial activities aiming to ensure that all services reaching the patient are safe, effective and acceptable.

Quality characteristics of medicines: identity, purity, potency, uniformity and bioavailability.

Quantitative data: data which describe the extent of a phenomenon in numerical terms.

Randomized controlled trial (RCT): a trial in which participants are randomly assigned to two groups: one (the experimental group) receiving the intervention that is being tested, and the other (the comparison or control group) receiving an alternative treatment or placebo. This design allows assessment of the relative effects of interventions.

Relative risk (RR): the number of times more likely (RR greater than 1) or less likely (RR less than 1) an event is to happen in one group compared to another. It is similar in concept to an odds ratio (OR), see above. Experimental designs which give rise to relative risk ratios include prospective studies with subgroups of predetermined sizes consisting of participants with and without the risk factor.

Relative risk reduction (RRR): the proportional reduction in risk between experimental and control participants in a trial. It is the complement of the relative risk (1-RR).

Statistically significant: means that the findings of a study are unlikely to be due to chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed result would occur by chance in only 1 in 20 similar studies. Confidence intervals (see above) can also be used to determine statistical significance. Where the word 'significant' or 'significance' is used without qualification in the test, it is being used in the statistical sense.

Systematic review: a review in which all the trials on a topic have been systematically searched for, appraised, and summarized according to predetermined criteria. It can, but need not, involve meta-analysis as a statistical method of adding together and numerically summarizing the results of the trials that meet minimum quality criteria.

Triage: a system whereby a group of casualties or other patients is sorted according to the seriousness of their injuries or illnesses so that treatment priorities can be allocated between them. In emergency situations it is designed to maximize the number of survivors.

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Appendices

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

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(*BMJ* 1998;317:625–629. Reproduced with permission from the BMJ Publishing Group).

Abstract

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

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

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

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

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

Introduction

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

Infection with HIV has changed the natural history of infection with *M tuberculosis*.⁴ People who are infected with HIV and who have a positive tuberculin skin test have a 30% or more

lifetime risk of developing active tuberculosis,⁵ and tuberculosis is the most common HIV related disease in developing countries.^{1,4} Thus, preventive treatment may be an important intervention to reduce the burden of tuberculosis in people infected with HIV, and their contacts, but its efficacy cannot simply be extrapolated from studies in people not infected with HIV.

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

Subjects and methods

Criteria for selecting studies for review

We included only randomised controlled trials that compared drug regimens aimed at preventing tuberculosis with placebo. Trials were considered irrespective of setting or target group, and we included all different drug regimens tested. Preventive treatment was defined as tuberculosis chemotherapy given to people who have a particular risk of developing tuberculosis. Particular risk refers to people who are infected with HIV and either infected with *M tuberculosis* (positive for purified protein derivative), or who are negative for purified protein derivative but live in a community where tuberculosis is endemic, or have a high risk of infection.⁶ Our definition of negative for purified protein derivative allowed inclusion of anergic patients (defined as a skin test reaction of < 5 mm to 5 tuberculin units, and < 2 mm reaction to mumps, tetanus toxoid, and candida antigen). In some instances we were unable to stratify outcomes by anergy in subjects negative for purified protein derivative as not all trials tested for it.

Search strategy

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

Review procedure

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

Outcome measures

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

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

Study (country)	Method	Participants	Interventions	Outcomes
Pape et al ⁹ (Haiti)	Randomised by computer Allocation not described Double blind*	Symptom free, newly diagnosed (n=118) No active tuberculosis (91/118 (77%) were women) Positive or negative for tuberculin†	Isoniazid 300 mg daily for 12 months	Subjects assessed every 3 months Mean follow up 33 months No loss to follow up
Hawken et al ¹⁰ (Kenya)	Block randomised by computer Allocation concealed Double blind‡	Mostly symptom free (n=684) No active tuberculosis Positive or negative for tuberculin	Isoniazid 300 mg daily for 6 months	356/509 (70%) of expected subjects seen at the end of the trial Median follow up 20 months
Gordin et al ¹¹ (USA; 74% New York)	Randomisation not described Allocation concealment not described No data on number of eligible patients not enrolled	HIV infected (119/517 (23%) had AIDS) Negative for tuberculin Anergic At high risk of tuberculosis	Isoniazid 300 mg daily for 6 months	326 (63%) patients completed treatment 6% and 7% of treatment and placebo groups were lost respectively Mean follow up 33 months
Whalen et al ¹² (Uganda)	Block randomised by computer Allocation concealed§ Double blind	Mild HIV disease (n=2736) Positive for tuberculin Anergic	Isoniazid 300 mg daily for 6 months then isoniazid plus rifampicin 600 mg daily for 3 months then isoniazid plus rifampicin plus pyrazinamide 2 g for 3 months Anergic: isoniazid 300 mg daily for 6 months	80–89% of the different groups completed the trials No data on follow up procedures Mean follow up 15 months

* Tuberculin as purified protein derivative.

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

‡ 12 of 696 enrolled patients were excluded and 14 of 684 failed to return after recruitment.

§ 9095 people were screened; 4306 (47%) did not complete baseline investigations and 2053 (23%) were ineligible.

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

Statistical analysis

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

Results

Included trials

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

Exclusion criteria were similar in all trials and included past history of tuberculosis, current tuberculosis, pregnancy, abnormal liver enzymes, and serious intercurrent illness. All treatment was self administered and adherence was monitored variously through self reporting, attendance at scheduled clinic appointments, and urine testing (both routine and unscheduled). No data on adherence were reported by Pape et al;⁹ Hawken et al reported that 31% of subjects missed at least 5 weeks' preventive treatment, and 70% had at least 50%

positive urine tests;¹⁰ Gordin et al reported that only 63% of patients completed preventive treatment within 6 months;¹¹ and Whalen et al reported that 75% of scheduled and 80% of unscheduled urine tests were positive.¹² Follow up was generally short, ranging from an average of 15 to 33 months (table). All trials were analysed by intention to treat.

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

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

In adults with a negative tuberculin skin test the estimates of effect in all trials included one, indicating non-significant results (fig). The pooled risk of tuberculosis in subjects with a negative tuberculin skin test who received preventive treatment was 0.82 (0.50 to 1.36) compared with placebo, confirming that no substantial protection was conferred by the intervention. Similarly, the pooled relative risk for mortality was 1.02 (0.89 to 1.17) confirming that no substantial protection was conferred by the intervention.

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

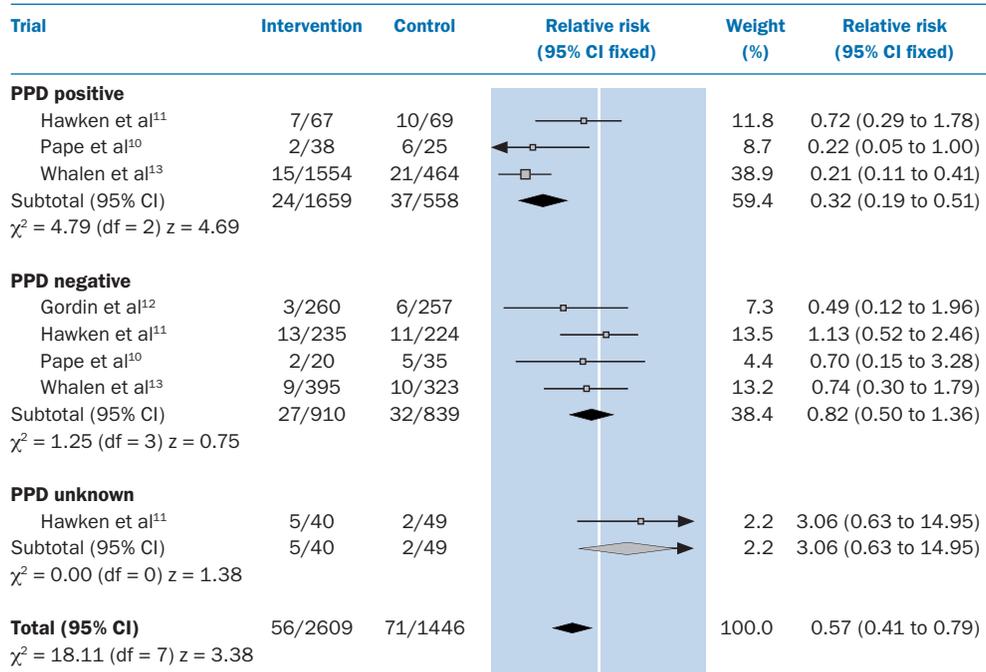
Discussion

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

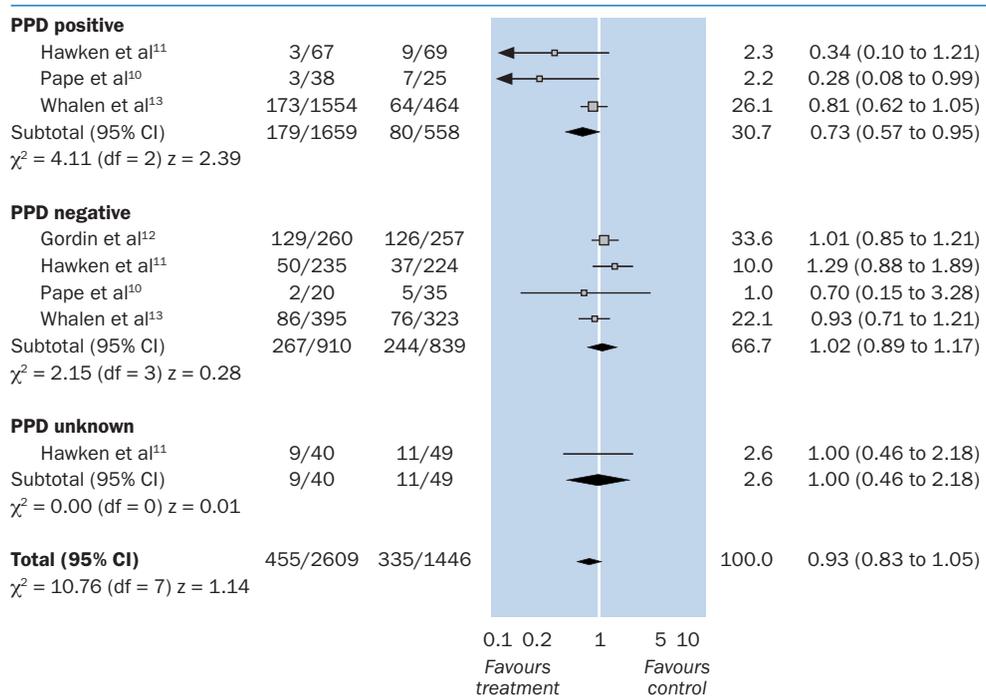
Thus, in settings where testing for purified protein derivative is possible, preventive treatment might best only be offered to adults infected with HIV with a positive tuberculin skin test. In settings where testing for purified protein derivative is not possible, if preventive treatment is given to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

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

No with active tuberculosis



No of deaths



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

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

Possible biases

A systematic review may be biased if trials reporting negative findings are not published. The trial reported to be incomplete¹³ published positive findings in abstract form, and the trial in preparation has also reported positive results. We found no statistical evidence of heterogeneity in this meta-analysis, but the power to detect heterogeneity was limited by

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

Key messages

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

It may be difficult to generalise our findings to all populations, as the baseline risk of tuberculosis varied substantially by setting. Gordin et al observed a very much lower incidence of tuberculosis than expected.¹¹ Preventive treatment works mainly by preventing reactivation of latent infection. Recent infection may account for 30–40% of the burden of tuberculosis in both developed¹⁵ and developing

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

Choice of drug regimen

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

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

Preventive treatment and tuberculosis control

Although reduction in individual risk of tuberculosis is substantial, unless a large proportion of the affected population receives preventive treatment it seems unlikely that this intervention will substantially reduce disease transmission in countries with a high tuberculosis prevalence. The priority for tuberculosis control remains the early detection and treatment of active cases. Preventive treatment may be a useful intervention for individuals and for targeted groups such as factory workers, hospital staff, police, and the armed forces¹⁷ who may have access to HIV testing, counselling, and ongoing care. These conclusions are in accord with current recommendations from the World Health Organisation and the International Union Against Tuberculosis and Lung Disease.¹⁸ This policy, and future refinements to it, can now be based on a body of systematically reviewed data from relevant trials that provides accurate estimates of effect, and that is constantly updated.¹⁹

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

This review is concurrently available on the infectious diseases module of the Cochrane Database of Systematic Reviews and will be updated as new data become available. We thank Dr Mark Hawken, who made original trial data available rapidly and courteously. Contributors: DW generated the idea for this review, developed the protocol, conducted the review, and wrote the paper; he will act as guarantor for the paper. SBS provided input on the protocol development and interpretation of the review and commented on the manuscript. PG was coordinating editor for the review and oversaw its quality throughout, provided methodological support, and commented on the manuscript. Funding: This work was funded by the South African Medical Research Council and a grant from the directorate: HIV/AIDS and sexually transmitted diseases of the department of health of the South African government. PG and the Cochrane Infectious Diseases Group are supported by the Department for International Development (UK) and the European Union. None of these bodies can accept any responsibility for the information provided in this review or for the views expressed.

Conflict of interest: None.

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APPENDIX 2

Example of pharmacoeconomic analysis: thrombolytics for acute myocardial infarction (a hypothetical exercise)

Hypothetical Medicines A and B have been compared in a randomized trial in which the primary outcome of mortality was measured 30 days after randomization.

Outcomes in 100 patients

No treatment	15 deaths
A	10 deaths
B	7 deaths

Drug cost per patient

A	US\$200
B	US\$1000

The assumed average survival following non-fatal myocardial infarction is 8 years.

Evaluate the available (hypothetical) evidence and decide which of two available medicines represents the more cost-effective choice.

How many lives could be saved if 1000 patients were treated with Medicine A, compared with no treatment? How many could be saved with Medicine B, compared with no treatment?

1000 patients treated with placebo: 150 will die.

1000 patients treated with A: 100 will die → 50 lives saved

1000 patients treated with B: 70 will die → 80 lives saved

What are the absolute risk (AR), the absolute risk reduction (ARR), the relative risk (RR), the relative risk reduction (RRR), and the number needed to treat to prevent one event (NNT) for death with Medicines A vs. B?

AR with A = $100/1000 = 0.1$; with B = $70/1000 = 0.07$

ARR (A versus B) = $0.1 - 0.07 = 0.03$

RR (B versus A) = $0.07/0.1 = 0.7$ (incidence of death with B is 0.7 × that with A)

RRR (B versus A) = $(0.1 - 0.07)/0.1 = 0.03 / 0.1 = 0.3 = 30\%$

NNT = $1/ARR = 33.3$ patients need to be treated with B to prevent one death

With a budget of US\$200 000, how many patients could be treated, and how many additional lives could be saved with each medicine, compared with no treatment?

A: $US\$200\ 000 / US\$200 \text{ p. patient} = 1000 \text{ pts treated} \rightarrow 50 \text{ lives saved}$

B: $US\$200\ 000 / US\$1000 \text{ p. pt} = 200 \text{ pts treated} \rightarrow 80 \times 200/1000 = 16 \text{ lives saved}$

What is the incremental cost per death avoided, for each of the thrombolytic agents, compared with no active treatment?

ICER (A versus placebo for 1,000 pts)

$$= \frac{(1000 \times \text{US\$}200 - 1,000 \times \text{US\$}0)}{50 \text{ lives saved}} = \frac{\text{US\$}200,000}{50} = \text{US\$}4000 \text{ per life saved}$$

ICER (B versus placebo for 1,000 pts)

$$= \frac{(1000 \times \text{US\$}1000 - 1000 \times \text{US\$}0)}{80 \text{ lives saved}} = \frac{\text{US\$}1000,000}{80} = \text{US\$}12\,500 \text{ per life saved}$$

What are the incremental cost-effectiveness ratios (ICERs), expressed as the incremental cost per life-year gained, for each of the medicines, compared with no active treatment? Assume 8 years survival per life gained.

1,000 patients treated with A → 50 lives saved. → 50 x 8 = 400 life years gained

ICER (A versus placebo for 1000 pts)

$$= \frac{(1000 \times \text{US\$}200 - 1000 \times \text{US\$}0)}{400 \text{ life years}} = \frac{\text{US\$}200\,000}{400} = \text{US\$}500 \text{ per life year gained}$$

1,000 patients treated with B → 80 lives saved → 80 x 8 = 640 life years gained

ICER (B versus placebo for 1000 pts)

$$= \frac{(1000 \times \text{US\$}1000 - 1000 \times \text{US\$}0)}{640 \text{ life years}} = \frac{\text{US\$}1\,000\,000}{640} = \text{US\$}1562.50 \text{ per life year gained}$$

What is the ICER for A compared to B (in terms of additional cost per additional life year gained?)

1000 patients treated with A → 50 lives saved. 1000 patients treated with B → 80 lives saved. 30 more lives are saved if we treat with B instead of A.

Assuming 8 years' survival per patient → 30 x 8 = 240 life years gained.

ICER (B versus A for 1000 pts)

$$= \frac{(1000 \times \text{US\$}1000 - 1000 \times \text{US\$}200)}{240 \text{ life years}} = \frac{\text{US\$}800\,000}{240} = \text{US\$}3333 \text{ per additional life year gained}$$

Note that this result is **NOT** the same as the difference between the ICERs for each medicine alone, compared to no treatment.

Answers to self-assessment questions, exercises and learning activities

Answers to self-assessment questions in Chapter 1, p.19

1. In what ways has pharmacy practice changed over the past 40 years?

Over the past 40 years, the pharmacist's role has changed from that of compounder and dispenser to one of "drug therapy manager". This involves responsibilities to ensure that wherever medicines are provided and used, quality products are selected, procured, stored, distributed, dispensed and administered so that they contribute to the health of patients, and not to their harm. The scope of pharmacy practice now includes patient-centred care with all the cognitive functions of counselling, providing drug information and monitoring of drug therapy, as well as technical aspects of pharmaceutical services, including medicines supply management. It is in the additional role of managing drug therapy that pharmacists can now make a vital contribution to patient care.

2. List the roles of the "seven-star pharmacist".

Care-giver, decision-maker, communicator, manager, life-long-learner, teacher and leader.

3. Differentiate among the terms pharmaceutical practice, pharmaceutical services and pharmaceutical supply.

Pharmaceutical practice includes the provision of pharmaceutical products, pharmaceutical services and pharmaceutical care, and covers all those activities and services provided by pharmacists in the health care system.

Pharmaceutical services: all the services rendered by pharmaceutical staff to support the provision of pharmaceutical care. Beyond the supply of pharmaceutical products, pharmaceutical services include information, education and communication to promote public health, the provision of drug information, regulatory services, education and training of staff.

Pharmaceutical supply aims to provide the correct medicines in the correct quantities and dosage forms, at reasonable prices and with recognized standards of quality. Activities at the level of supply management include manufacture, distribution and dispensing of medicines. In many settings, especially the institutional one, they are still seen as the pharmacist's main responsibility. They remain important, as the availability of medicines is a prerequisite for any pharmaceutical care.

4. Identify the three components of quality assurance in health care in your working environment.

Donabedian defined the three elements of quality assurance in health care as structure, process and outcome.

Structure – e.g. individual patient care in a practice setting, institutional patient care, national committee or executive body

Process – e.g. provision of drug therapy, counselling, monitoring of treatment; provision of quality medicines, e.g. through manufacture, distribution and/or dispensing; provision of drug information or education

Outcome –patients’ improved or maintained quality of life e.g. through positive therapy outcomes, through the provision of quality medicines, or through the provision of information and education

Answers to Learning Activity 3.5, p.52 (based on systematic review by D. Wilkinson et al.)

Clear review question stated (question type*, population, intervention and outcome)?	Yes – Question type: Prevention; therapy (preventive) Population: Adults infected with HIV Intervention: preventive treatment for tuberculosis Outcomes: 1. Frequency of TB, 2. Overall mortality
Included study designs stated?	Yes – Randomized controlled trials only (see Subjects and Methods, Criteria for selecting studies for review)
— Criteria used to assess the quality of studies	(See Review procedure): “The quality of each trial was graded using predefined criteria, assessing method of allocation sequence generation, allocation concealment, inclusion of all randomised participants, follow up of subjects, and analysis by intention to treat.”
— Study characteristics documented for included studies?	Yes (see Table 1)
Inclusion/exclusion criteria stated?	Yes – (see under Criteria for selecting studies for review): “We included only randomised controlled trials that compared drug regimens aimed at preventing tuberculosis with placebo. Trials were considered irrespective of setting or target group, and we included all different drug regimens tested. Preventive treatment was defined as tuberculosis chemotherapy given to people who have a particular risk of developing tuberculosis. Particular risk refers to ...” (etc.) (Review procedure): “Trials considered for inclusion were examined to determine completeness of reporting.” ... “Authors of incomplete or abstracted trials were contacted for further details.” (see Results): “Exclusion criteria were similar in all trials and included past history of tuberculosis, current tuberculosis, pregnancy, abnormal liver enzymes, and serious intercurrent illness.”
Literature search strategy recorded?	Yes – (see Search strategy) “We searched Medline using the search terms HIV, tuberculosis, preventive therapy, and chemoprophylaxis. We also searched the Cochrane Controlled Trials Register, the most comprehensive source of controlled trials (disk issue 1, 1998). In addition, we searched references of all retrieved articles and contacted relevant researchers to ensure that all completed trials had been identified.”

Data abstracted in a manner consistent with the review question?	Yes – see definition of outcomes given under Outcome measures. The presence of active TB was defined in several ways (microbiologically, histologically, clinically) Results were stratified by PPD status where possible
Reproducible and bias-free process of — identifying studies? — including studies? — abstracting data?	Yes — Comprehensive search strategy — Clear inclusion criteria appropriate to the type of review question; efforts were made to obtain data for studies where results were incomplete — Clearly and appropriately defined outcomes, one researcher abstracted data, another checked collated data (see Review procedure) See paragraphs on possible biases. Information on contributors and funding included; no declared conflicts of interest (last paragraphs before references)
Relevant, justifiable bottom line ?	Yes – TB infection and mortality are relevant endpoints; stratification by PPD status allowed conclusions for subgroups; relatively brief follow-up times are discussed as a limitation (see Discussion)
Meta-analysis for different outcomes used (appropriately)?	Yes – Results were analysed with approved methodology – relative risk, 95% confidence intervals, weighting of individual trials according to sample size and trial quality (see table)
Up-to-date ?	Yes – study accepted for publication in July 1998; Publications of that year are included in the list of references

Question types: therapy, diagnosis, prognosis, aetiology/harm, prevention, screening, quality improvement, economic

Answers to Learning Activity 3.6, p.58 (cost-effectiveness of nevirapine for prevention of mother-to-child transmission of HIV)

	Universal programme	Targetted programme
Number of pregnant women in the hypothetical cohort	1000	1000
Number of HIV-positive pregnant women treated	300	240
Cost of programme for the hypothetical cohort (treating all pregnant women, or screening all pregnant women and treating those found HIV-positive)	1000 x US\$4 = US\$4000	1000 x US\$6 = US\$6000 + 240 x US\$4 = 960 Total US\$6960
Benefit: Number of infections averted in the hypothetical cohort	30	24
Cost/benefit ratio: Cost per infection averted	US\$4000/30 = US\$133	US\$6960/24 = US\$290
Incremental cost/benefit ratio: Difference (per infection averted) (Note that the benefit of the targeted approach achieved by avoiding adverse events with nevirapine in healthy pregnant women has not been included in this calculation.)	US\$290 – US\$133 = US\$157 The universal programme costs US\$157 less per infection averted than the targeted programme.	

However, good pharmacy practice/pharmaceutical care concept is new to many of the community pharmacists working in many of the developing countries. Moreover, there are many barriers to implementing this concept into practice.²⁹ Lack of time, lack of understanding, lack of training, and resource constraints are the main barriers.Â Patient counseling by pharmacist â€“ a focus on chronic illness. Pak J Pharm Sci. 2006;19(1):62â€“65.