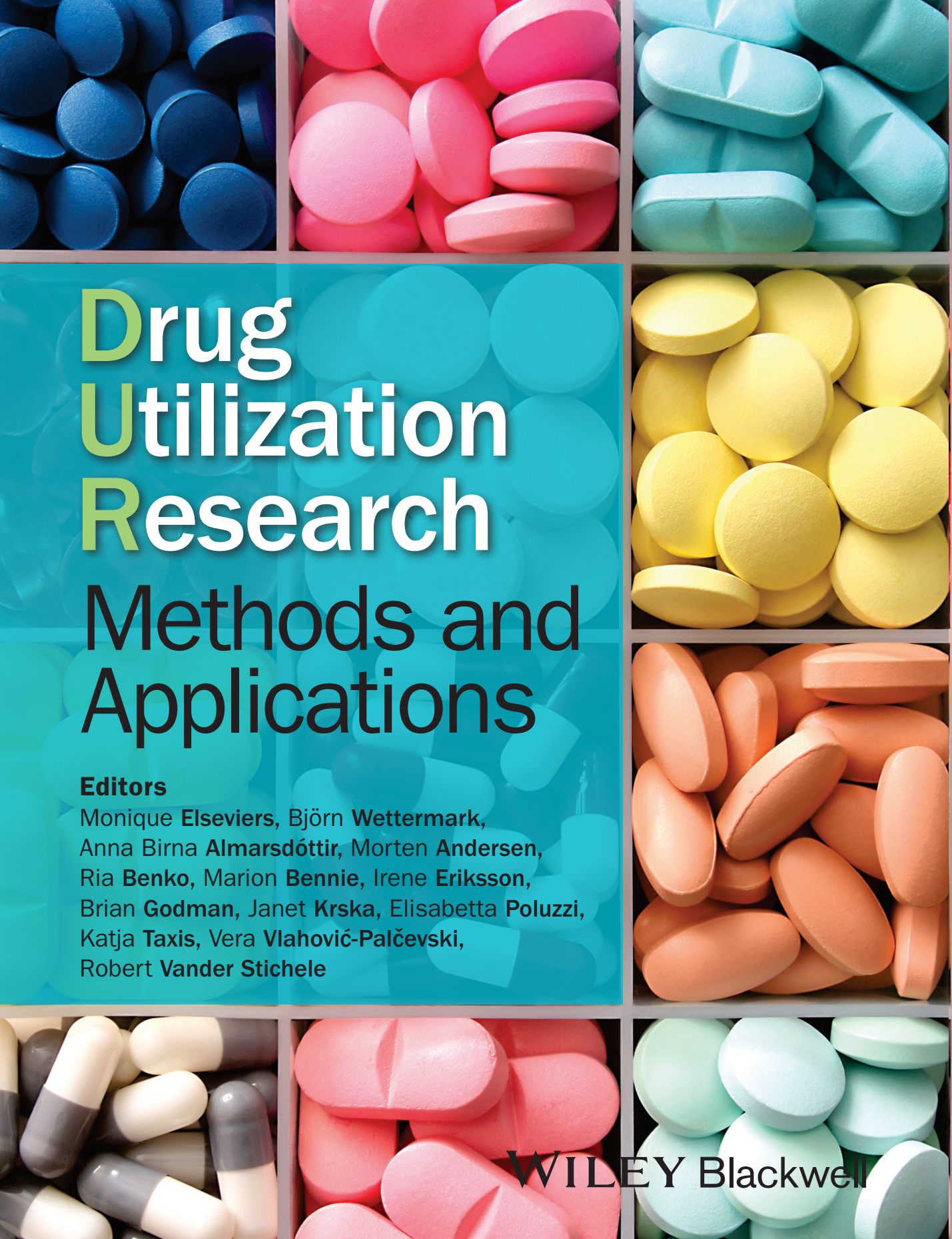

Drug Utilization Research

Methods and Applications

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About the companion website

This book is accompanied by a companion website:

www.wiley.com/go/elseviers/drug_utilization_research

The website includes:

- References and further reading
- A large version of Figure 34.2
- Appendix to Chapter 11

PART 1
Introduction

CHAPTER 1
Introduction to drug utilization research

Björn Wettermark[1], Monique Elseviers[2], Anna Birna Almarsdóttir[3], Morten Andersen[1], Ria Benko[4], Marion Bennie[5], Irene Eriksson[1], Brian Godman[6], Janet Krska[7], Elisabetta Poluzzi[8], Katja Taxis[9], Robert Vander Stichele[10] & Vera Vlahović-Palčevski[11]

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KEY POINTS

- Drug utilization research can be defined as 'an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes'.
- The discipline may be seen as the bridge between pharmacoepidemiology and health services research. It is also closely connected to clinical pharmacology, with the principal aim of drug utilization research being to facilitate the safe and effective use of medicines in populations.
- Research in drug utilization began to develop in the 1960s. Some pioneering studies focused on assessing differences in drug utilization between countries or regions. Other studies focused on factors influencing the prescribing patterns of physicians.
- The eclectic nature of drug utilization research requires expertise in a broad range of research methodologies. Part 2 of the book provides guidance on a wide range of quantitative and qualitative methods used in drug utilization research.
- The numerous applications of drug utilization research are illustrated in Part 3, which include sections on comparative drug utilization research, drug utilization and health policy, drug utilization in specific populations and therapeutic areas, determinants of drug utilization, adherence and drug utilization research, the role of drug utilization within the field of pharmacoepidemiology and the assessment and improvement of the quality of medicine use.

Room for improvement in drug utilization

Medicines play an important role in the provision of optimal care and have a major impact on health. During the last decades of the 20th century, new medicines have markedly decreased mortality, shortened hospitalization duration and improved quality of life for millions of people [1,2]. However, it is also important to recognize the negative consequences of drug therapy and the emerging problem of inappropriate drug use, with issues ranging from increased morbidity and mortality to excessive medicalization, polypharmacy, adverse drug reactions (ADRs) and increased antimicrobial resistance.

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The economic consequences associated with inappropriate drug use are considerable. The average treatment cost for a single ADR in Germany has been estimated at approximately €2250, equating to €434 million per year [3]. Drug-related hospital admissions have been assumed to account for more than 4% of the total health expenditure in Great Britain [4]. In the United States, the incremental expenditure related to inappropriate use of medicines in the community-dwelling elderly was estimated at $7.2 billion in 2001, and these costs are likely to have increased over time [5]. Other researchers have suggested that for every dollar spent on medications, one additional dollar is needed to correct problems caused by inappropriate use of medicines [6].

The extent of inappropriate use of medicines may be even greater in low- and middle-income countries. Common problems include overuse of drugs such as antibiotics and antidiarrhoeals, polypharmacy and the prescribing of inappropriate drugs (e.g. those with limited efficacy or an uncertain safety profile). In many of these countries, up to 60–80% of health problems are self-medicated and poor adherence to doctors' prescriptions is common [7].

Medicines are also important from an economic perspective. Internationally, there is increased scrutiny of pharmaceutical expenditures, and medicines have been the most rapidly growing cost component in ambulatory care in most countries [8–13]. Challenges in financing drugs may be an even greater concern in low- and middle-income countries, where medicines can account for up to 60% of total health care spending [14]. The reasons behind the increasing expenditure on medicines include demographic changes, the continued launch of new expensive medicines, rising patient expectations and stricter clinical targets [9,15,16].

The history of drug utilization research

The emerging problems of rising expenditure and inappropriate use of medicines clearly demonstrate the need for drug utilization research, a cross-disciplinary and multiprofessional science that aims to describe and understand the use of medicines in society. Research in drug utilization began to develop in the 1960s. The pharmaceutical industry early on expressed the need for drug utilization data that could be used to monitor the performance of its representatives, serve as a basis for marketing and define areas for future drug development and research. This laid the basis for the development of large, commercial databases capable of tracking the prescribing and sales of medicines; Intercontinental Marketing Services (IMS) was one of the pioneers [17]. At the same time, concern about pharmaceutical expenditures stimulated the development of public statistics on drug use, independent of those produced by pharmaceutical companies for marketing purposes. These statistics were initially compiled to allow informed financial, administrative and reimbursement decisions, but they were also valuable for research, assessment of the quality of prescribing and quantification of the risks and benefits of drug use in the population. The extent and nature of these early databases varied substantially between countries; in the beginning, they were mostly based on data collected from wholesalers or health authorities. In recent decades, technical development has facilitated the establishment of large databases in many countries across the world.

The pioneering drug utilization studies in Europe focused on assessing differences in drug utilization between countries or regions [18–21]. Other studies focused on factors influencing the prescribing patterns of physicians [22–24]. In 1969, the World Health Organization (WHO) organized its first meeting on Drug Consumption in Oslo, where researchers expressed the need for a common medicines classification system and for a technical unit of comparison in drug utilization studies [19]. As a result, scientists, mainly from Northern European countries, came together in an informal group and developed a new unit of measurement, initially called the 'agreed daily dose', but subsequently named the 'defined daily dose' (DDD) [20,21,25]. In 1975, the Norwegian agency Norsk Medisinaldepot published a list of DDDs of medicines registered in Norway, which were classified according to the European Pharmaceutical Market Research Association (EPhMRA) code, with the addition of two chemical subgroups. The invention of the Anatomical Therapeutic Chemical (ATC) classification system and the DDDs enabled cross-national comparisons of drug utilization and was of key importance for the future development of the discipline [25].

In 1976, a small group of scientists active in these areas established the informal Drug Utilisation Research Group (DURG). For approximately 20 years the WHO Regional Office for Europe served as the group's secretariat, and, consequently, the DURG was often referred as the 'WHO-DURG'. From 1993, the relationship between the

DURG and the WHO loosened, as the latter was unable to further provide secretarial functions. Consequently, in 1994, an independent European Drug Utilisation Research Group (EuroDURG) interim committee was elected, and, in 1996, at a meeting at Lake Balaton, EuroDURG was formally established [26,27]. The EuroDURG mission stated that drug utilization research should not only provide information on sales of medicines but also facilitate exploration of other questions related to the safe and effective use of medicines, such as:

- Why are drugs prescribed?
- Who prescribes drugs and for whom?
- Do patients take drugs correctly?
- What are the benefits and risks of prescribed drugs?

A number of topics for drug utilization studies have been suggested over the years [27,28], as illustrated in Box 1.1.

Drug utilization research developed quickly and became a common subject at international conferences in clinical pharmacology, pharmacy and epidemiology. Some important milestones and events in the development of drug utilization research are shown in Figure 1.1.

During the 1976 DURG meeting in Copenhagen, it was proposed that the WHO should sponsor a publication on guidelines for performing basic drug utilization studies. At the DURG meeting in 1977, the WHO Regional Office in Copenhagen reaffirmed its interest in publishing such guidelines, and in 1979 the first book was published [21]. A number of other pivotal papers and handbooks have been written throughout the years, describing concepts and methods used in the field [17,29–37]. The issue of prescribing quality has always been an area of interest for drug utilization researchers, and, in 2004, the Drug Utilization Research Quality Indicator Meeting (DURQUIM) was held with the aim of defining a taxonomy, constructing a conceptual framework, examining the validity and discussing the use of prescribing quality indicators [38].

Drug utilization research also developed rapidly outside of Europe. In the United States, the early development of the discipline was largely driven by federal government initiatives, with the purpose of curbing Medicaid expenditures while maintaining quality of care [39]. Further development included the instigation of a number of drug utilization review programmes in various institutions, as well as in ambulatory care [40,41]. Early drug utilization studies were conducted by drug information centres, aimed at increasing awareness of the risks and benefits of new, existing or combined uses of medicines [42,43]. Since 1992, the Agency for Healthcare Research

Box 1.1 Aspects and consequences of drug utilization to be explored.

Medical

Benefits: efficacy in preventing, relieving and curing diseases or their symptoms and complications.

Risks: short-term and long-term adverse effects, special risk factors associated with genetics, disease and environment, nutrition, age, sex, pregnancy, lactation, etc.

Benefit/risk ratio: the extent to which inappropriate prescribing or use may reduce benefits and increase risks.

Social

Attitudes to drugs and health and their basis: current trends in the 'drug culture' versus persistent or resurgent use of traditional medicines.

Drug abuse and dependence and their causes and trends.

Improper use of drugs (noncompliance, use of drugs for purposes for which they were not prescribed or recommended): incidence and explanation.

Discrimination and social injustice (e.g. unavailability of important drugs to those who need them).

Effect of information and regulatory measures.

Economic

Drug and product prices and costs; imports versus local production; costs of new drugs versus old drugs and of specialities versus generic products; costs of drug versus non-drug treatment.

Drug cost/effectiveness/safety ratios for all the comparisons listed above.

Current and future allocation of national resources (money, personnel, facilities) to the drug and health budget.

Source: Baksaas and Lunde 1986 [28]. Reproduced with permission from Elsevier.

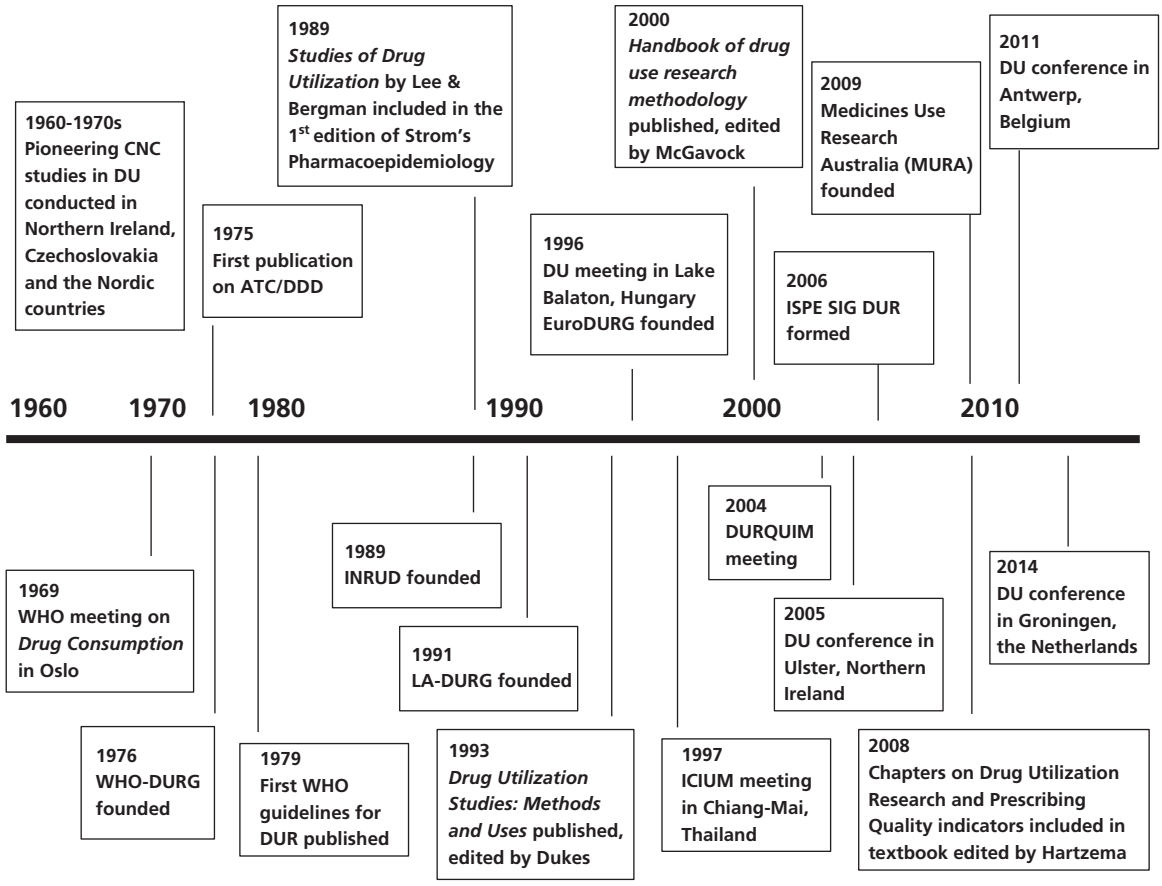

Figure 1.1 Milestones and events in the development of drug utilization research. ATC/DDD, the Anatomical Therapeutic Chemical Classification System with Defined Daily Doses; DU, drug utilization; CNC, cross-national comparison; DURQUIM, Drug Utilization Research Quality Indicator Meeting; EuroDURG, European Drug Utilization Research group; ICIUM, International Conference on Improving the Use of Medicines; INRUD, International Network for Rational Use of Drugs; ISPE, International Society for Pharmacoepidemiology; LA-DURG, Latin American Drug Utilization Research group; SIG, Special Interest Group; WHO, World Health Organization; DURG, Drug Utilization Research Group; DUR, Drug Utilization Research.

and Quality (AHRQ) has funded drug utilization studies through a collaboration of the Centers for Education and Research on Therapeutics (CERTs). Today, the CERTs programmes conduct research and provide education to advance the optimal use of all therapeutics in order to address the limited comparative information on the risks, benefits and interactions of new and older products and to provide guidance to health professionals on the appropriate and cost-effective use of drugs [44].

In Latin America, a network for drug utilization (LA-DURG) was founded in 1991 at the first meeting of Latin American groups for drug epidemiology, held in Barcelona [45]. Participants at the meeting expressed concern that Latin American drug utilization data were scarce and fragmented across the continent. Local authorities were unable to guarantee the effectiveness and safety of products marketed and had no access to quantitative or qualitative drug utilization data [45]. The few drug utilization studies conducted showed serious problems around the inappropriate prescribing, dispensing and use of medicines. Consequently, the importance of drug utilization research to informing rational drug policy at both national and local levels was recognized.

Drug utilization research also developed in Australia, Asia and Africa [46]. In the early 1990s, the WHO and the International Network for the Rational Use of Drugs (INRUD) published a simple sampling method

and a standard set of indicators to describe core aspects of prescribing and dispensing [47]. The first International Conference on Improving the Use of Medicines (ICIUM), held in Chiang-Mai, Thailand, in 1997, systematically reviewed the interventions in developing countries [47]. Considerable research gaps in the understanding of safe and effective medicines use were identified, and it was suggested that more research should be directed to promoting the rational use of medicines across multiple settings, including hospitals, the private sector and the community. A number of key areas were also identified for future research, such as interventions to improve the use of antibiotics and antimalarial drugs, methods to assess the impact of drugs and therapeutic committees and the impact of financial incentives on drug utilization patterns.

Over the years, drug utilization research has continued to grow, and a Medline search run in 2015 using the term 'drug utilization' gave more than 20 000 hits. In addition, several thousand drug utilization studies can be found under other search terms related to the prescribing, dispensing and consumption of medicines. Although there has been an explosion in the availability of data and the development of methods, the research questions raised by EuroDURG in 1969 are still relevant in summarizing the important aims of drug utilization research.

It is also important to acknowledge the commonalities in the development of drug utilization research and pharmacoepidemiology. In 1985, the first International Conference on Linked Databases was held in the United States. The name of the conference was subsequently changed to the International Conference on Pharmacoepidemiology (ICPE), and, in 1989, during the fifth conference in Minneapolis, the International Society for Pharmacoepidemiology (ISPE) was officially launched. Many drug utilization researchers joined the society, and drug utilization studies constituted a large proportion of the presentations at all annual conferences. In 2006, a special interest group in Drug Utilization/Health Service Research (SIG DUR/HSR) was formed within ISPE with the aim of creating a global forum for discussion and cooperation between drug utilization researchers in different continents. EuroDURG merged with ISPE and became the European branch of the special interest group. In 2012, EuroDURG, in collaboration with ISPE SIG DUR/HSR, decided to develop *Drug Utilization Research*: *Methods and Applications* for use by researchers, academics and policymakers active in the field.

Definition and delineation

In 1977, the WHO defined drug utilization research as 'studies on the marketing, distribution, prescription and the use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences' [48]. However, this definition does not fully capture the depth and breadth of drug utilization, and, in 2008, a more extensive one was proposed in the textbook *Pharmacoepidemiology and Therapeutic Risk Management* [37]:

> Drug Utilization Research is an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes.

Drug utilization research focuses on various medical, social and economic aspects of drug use. Medical consequences include the risks and benefits of drug therapy, while social aspects can be related to inappropriate use. Economic issues deal with the cost of medicines and treatment for patients and society. These areas are described in Box 1.1.

The WHO definition of drug utilization places the research area close to a number of related research fields. The greatest commonality lies with pharmacoepidemiology, which is defined as 'the study of the utilization and effects of drugs in large numbers of people' [49]. The main difference between drug utilization research and pharmacoepidemiology is that the latter focuses to a greater extent on the assessment of quantitative risks (and, recently, also benefits) of drug treatment in cohorts of patients, mostly followed in databases. Drug utilization research, on the other hand, focuses on the quantity and quality of medicine use in different countries, regions and settings, and the explanatory factors behind these patterns (Figure 1.2).

Another way to describe the difference between the two research fields has been suggested by Bergman: 'While drug utilization studies employ various sources of information focusing on drugs, e.g. wholesale and prescription registers, the term "epidemiology" implies that pharmacoepidemiological studies are population based, and link health events to drug exposure' [50]. Over time, the distinction between the two terms has diminished, and they are sometimes used interchangeably. This interplay between the two fields is illustrated in a bibliometric study on the scope and range of drug

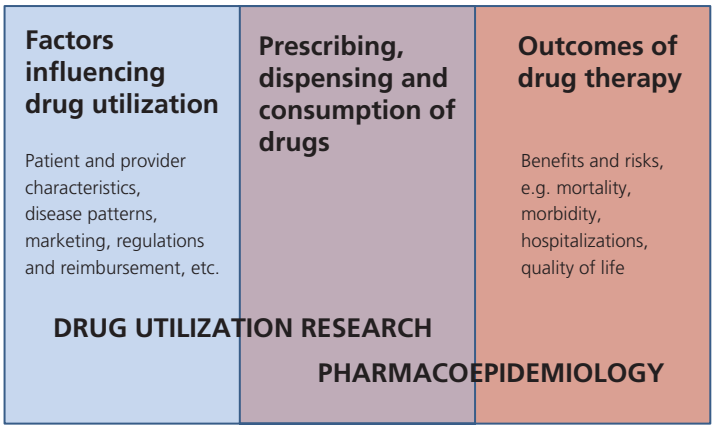

Figure 1.2 Traditional descriptions of drug utilization research and pharmacoepidemiology.

utilization research abstracts presented at the International Conference on Pharmacoepidemiology [51].

The current definition of drug utilization research illustrates the broad nature of the field, which includes both quantitative and qualitative studies. It also emphasizes that intervention studies aimed at improving drug utilization are an important part of the discipline. Thus, it links drug utilization research to health services research. The latter has been defined as 'a multidisciplinary field of inquiry, both basic and applied, that examines the use, costs, quality, accessibility, delivery, organization, financing, and outcomes of health care services to increase knowledge and understanding of the structure, processes, and effects of health services for individuals and populations' [52]. Consequently, drug utilization research may be seen as the bridge between pharmacoepidemiology and health services research (Figure 1.3).

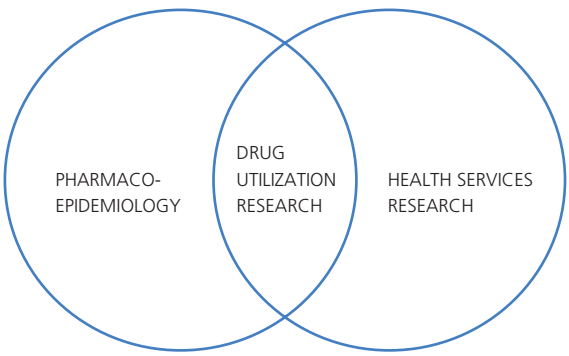

Figure 1.3 Drug utilization research as a bridge between pharmacoepidemiology and health services research.

Drug utilization research is also connected to the discipline of clinical pharmacology. Researchers in this field study pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body). The original aims of clinical pharmacology were to develop new medicines and to determine the balance between drug benefit and risk in clinical trials. In recent years, the scope of clinical pharmacology has widened to include exploration of drugs as therapeutic agents and assessment of the beneficial and adverse effects of the use and the deliberate misuse of drugs [53]. Clinical pharmacology has a strong focus on pharmacovigilance activities, such as the reporting, collecting and evaluation of ADRs; however, clinical pharmacologists are also engaged in promoting rational drug use through medical education, drug information centers, therapeutic drug monitoring services and drug and therapeutic committees.

While clinical pharmacology studies the 'absolute' efficacy of a drug in clinical trials under ideal conditions, drug utilization research and pharmacoepidemiology study the 'real-world' effectiveness of medicines and attempt to identify and quantify risks that are difficult to observe or assess in clinical trials or spontaneous reporting systems. Furthermore, drug utilization research includes assessment of the appropriateness of drug use and expenditure.

There are a number of other scientific disciplines that share relationships with drug utilization research, as shown in Table 1.1. The interplay with some of these disciplines is further described in Part 3, Section G.