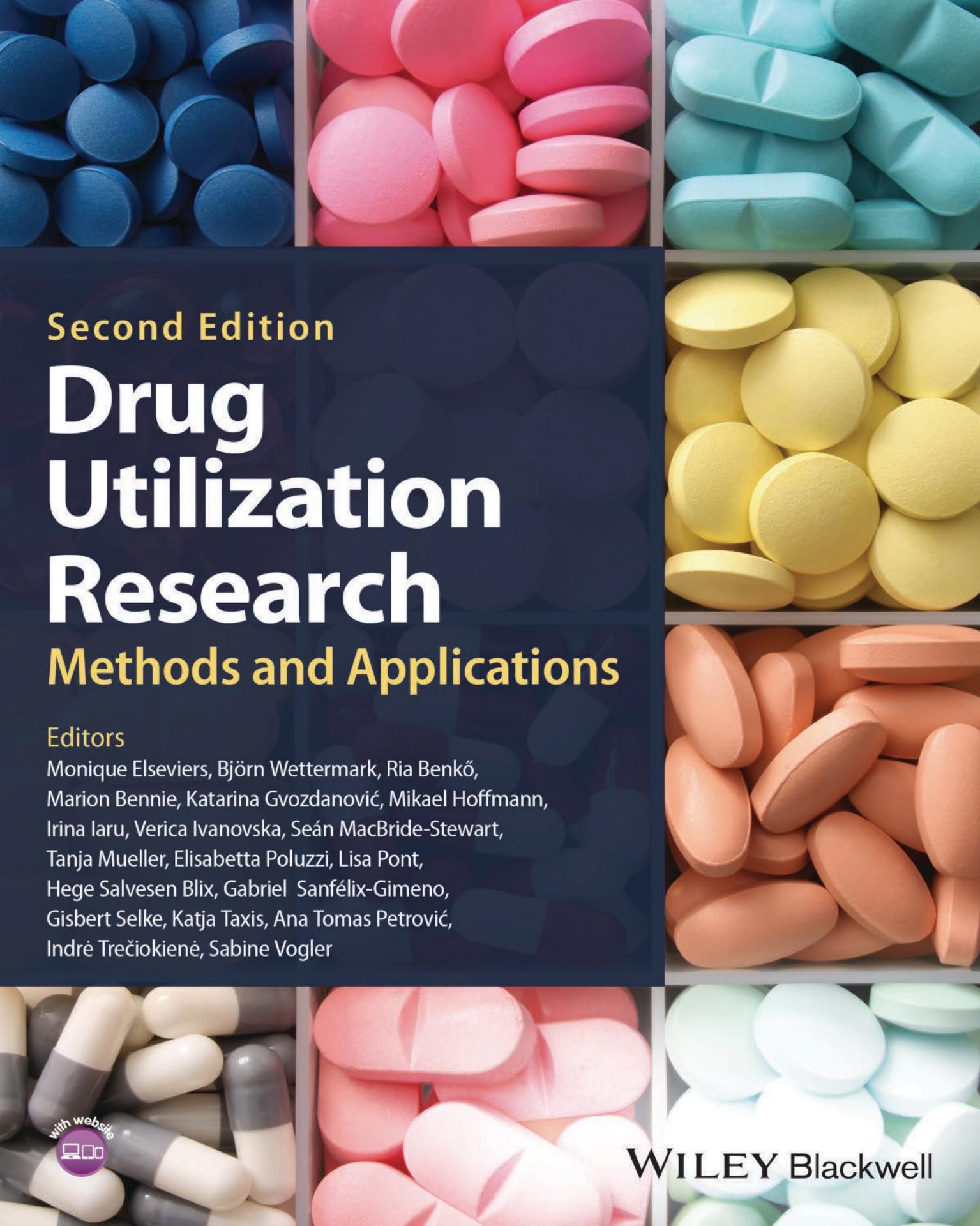

Second Edition

Drug Utilization Research

Methods and Applications

Editors

Monique Elseviers, Björn Wettermark, Ria Benkő, Marion Bennie, Katarina Gvozdanović, Mikael Hoffmann, Irina Iaru, Verica Ivanovska, Seán MacBride-Stewart, Tanja Mueller, Elisabetta Poluzzi, Lisa Pont, Hege Salvesen Blix, Gabriel Sanfélix-Gimeno, Gisbert Selke, Katja Taxis, Ana Tomas Petrović, Indrė Trečiokienė, Sabine Vogler

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Preface to the second edition

One decade ago, the European Drug Utilization Research Group (EuroDURG) took the initiative to prepare a book entitled *Drug Utilization Research: Methods and Applications*. Rather than limiting this work to a handbook focusing only on the methodological issues of Drug Utilization Research (DUR), it was our intention to also offer a complete overview of the different applications of DUR, ranging from DUR and health policy over DUR in specific areas and populations to DUR applications in the broader field of pharmacoepidemiology and strategies to improve the quality of prescribing.

Since the field of DUR has experienced a major expansion during the last decade, the necessity for an update of the first edition was emerging. Additionally, the need for a comprehensive educational handbook gained interest in a broader field of academic researchers, civil service workers, health insurances and health authorities, since more researchers have the opportunity to work with available DU data that wait to be analyzed to support policy decisions.

The preparation of this second edition of the DURbook started in 2020 with the distribution of a questionnaire offering more insight into who was using the book (83% were academic researchers), the reason for using the book (mainly as a reference work and for teaching material) and the need to publish the second edition in digital as well as printed format. Furthermore, we received the suggestion to add a new part focusing on the current state of drug utilization research at the global level. Using the contacts of the Special Interest Group of DUR (SIGDUR) of the International Society of Pharmacoepidemiology (ISPE), we were able to assemble testimonies of initiatives in DUR from across the world.

This new edition consists of four overarching sections: introduction, methods, applications and the new fourth section on the globalization of DUR. New chapters were added handling, e.g., aggregate level analyses of DU data, artificial intelligence/machine learning, ethical aspects in DUR, and environmental pharmacoepidemiology. In the previous edition, the application section was mostly a collection of published research. The updated content focusses on specific challenges, and expands on how to deal with these, keeping in mind the educational purpose of the book. In contrast with the previous edition, we have been able to add 30 key references to each chapter, hosting this time only the additional references online.

The making of this second edition followed a strict organizational pattern. The editorial board (EB) met virtually on a monthly basis. Two EB members were assigned to each section of the book. They were responsible for the communication with the authors of their chapters, discussing the content, keeping deadlines, and having a first critical reading of the delivered chapters. A further internal review of each chapter was mainly completed during hybrid DURbook weekends organized at the universities of Vilnius, Copenhagen, Uppsala, Bologna and Antwerp (see acknowledgement). After revision, based on the comments of section leaders and internal reviewers, an updated version of each chapter was sent for further comments to one or two external reviewers not involved in the development of the book (see list of external reviewers).

Drug utilization research is passing through a remarkable period of conceptual development. Although we attempted to incorporate the most up-to-date knowledge in this field, we are aware about possible gaps in our descriptions, about incompleteness and imperfections. Nevertheless, we hope that this second edition of the DURbook will become a helpful tool and a source of inspiration for all researchers working with drug utilization data.

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This second edition of the DURbook is built on the experience and content of the previous one. We remain grateful to all editors and authors that were no longer involved in the creation of this second edition but contributed substantially to the first edition.

We appreciate the utmost importance of the involvement of our **62 external reviewers**. With their independent evaluations and constructive comments, they contributed considerably to improve the quality of each chapter (see list of external reviewers). Special thanks go to Tanja Mueller for her administrative help and persistent efforts to find and contact the most suitable specialists in the field for performing these external reviews.

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About the companion website

This book is accompanied by a companion website:

www.wiley.com/go/elseviers/drug_utilization_research2e

The website includes:

- Full References List

PART 1

Introduction to drug utilization research

CHAPTER 1
Introduction to drug utilization research

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KEY MESSAGES

- Drug utilization research (DUR) can be defined as "Quantitative and qualitative studies to describe, evaluate, understand and improve the use of medicines".
- The discipline may be seen as the bridge between pharmacoepidemiology and health services research. The principal aim of DUR is to facilitate the safe and effective use of medicines in different populations and the society.
- 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. These are still important areas of inquiry in DUR.
- The eclectic nature of DUR requires expertise in a broad range of research methodologies. Part 2 of the book provides guidance on several quantitative and qualitative methods used in drug utilization research.

Drug Utilization Research: Methods and Applications, Second Edition. Edited by Monique Elseviers.

Companion Website: www.wiley.com/go/elseviers/drug_utilization_research2e

- The numerous applications of DUR are illustrated in Part 3, which include sections on health policy, comparative drug utilization studies, drug utilization in specific populations and therapeutic areas, medication adherence, the role of drug utilization within other scientific fields, and the assessment and improvement of the quality of medicine use.
- The nature of the scientific questions and the types of drug utilization studies vary across the world. This is illustrated in Part 4 of the book where researchers from all over the world describe the state of the art in DUR in their region.

The importance of drug utilization research

Medicines have a major impact on health and are essential for the provision of optimal care. The introduction of antibiotics in the 1940s drastically changed medicine. In addition to treatment of infectious diseases, these drugs also enabled many modern medical procedures. During the last decades of the 20th century, new medicines further decreased mortality, shortened hospitalization duration, and improved quality of life for millions of people [1]. The first decades of the 21st century have brought further advances in drug therapy with the introduction of many new biologicals and targeted treatments for cancer, orphan diseases, and other areas of high unmet medical need [2].

However, it is also important to recognize the negative consequences of drug therapy both for individual patients and society. The emerging problem of inappropriate drug use brings issues ranging from increased morbidity and mortality to unnecessary medicalization, adverse drug reactions and increased antimicrobial resistance. The World Health Organization (WHO) estimated that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly [3]. The economic consequences are considerable. The most important contributor is poor medication adherence which has been estimated to be associated with almost 200,000 deaths annually and €80–125 billion avoidable costs in the European Union [4].

Problems with irrational use of drugs may be even greater in developing countries. Common problems include overuse of drugs such as antibiotics and antidiarrheals, inappropriate use of injections, polypharmacy, and the prescribing of inappropriate drugs with, for example, limited efficacy or an uncertain safety profile in certain patient groups [5]. Before the COVID-19 pandemic, it was estimated that two billion people lacked regular access to essential medicines [6]. The challenges became even worse during the pandemic with reports of shortages in supplies, hoarding of medicines, and the circulation of falsified medicines [7].

Drugs are also important from an economical perspective. During the last decades of the 20th century, medicines accounted for the most rapidly growing cost component in ambulatory health care in most countries [8–11]. Pressure is even higher on health-care systems in low and middle income countries, where between 20 and 60% of total healthcare spending is allocated to medicines [12]. The reasons behind the increasing expenditures on medicines are well known and include demographic and morbidity changes, the continued launch of new expensive medicines, rising patient expectations, and stricter clinical targets [9, 13]. As a response, many countries implemented large demand-side reforms to promote higher use of generics and more cost-effective introduction of new medicines [14, 15].

Finally, there are also environmental consequences of the use of drugs. A recent review found concentrations of active pharmaceutical ingredients at levels posing a threat to environmental and/or human health in more than 25% of 1052 sampling sites in 258 rivers across 104 countries [16]. The term sustainability is increasingly used in the public debate, stressing the importance of meeting today's needs without jeopardizing the ability of future generations to meet their needs (Brundtland Commission 1987). Sustainability is typically being described as having three dimensions; economic, social and environmental – all of which are equally important for the development towards a sustainable future. Rational use of drugs is closely linked to all these three aspects.

The history of drug utilization research

The emerging problems of rising expenditure and inappropriate use of drugs clearly demonstrates the need for drug utilization research, a multi-professional science which aims to describe, evaluate, understand, and improve the use of medicines. Research in drug utilization began to develop in the 1960s. The pharmaceutical industry expressed the need for drug utilization data to monitor the performance of their representatives early on, to serve as a basis for marketing as well as to define areas for future drug development and research. This laid the basis for the development of large, commercial databases for tracking prescribing and sales of medicines with Intercontinental Marketing Services (IMS, now IQVIA) as

one of the pioneers [17]. At the same time, concern about drug expenditures stimulated the development of public statistics on drug use, independent of those produced by drug companies for marketing purposes. These statistics were initially compiled to allow informed financial, administrative and reimbursement decisions, but at the same time data were also made available for research. The extent and nature of these early databases varied substantially between countries, and in the beginning they were mostly based on data collected from wholesalers or reimbursement agencies. During the last decades technical development has facilitated the establishment of large registries in many countries across the world (see further in the chapter on secondary data sources 2.9). The initial databases were to a large extent created to fulfill financial needs. However, they also proved to be valuable tools for analyses of the quality of prescribing and to assess the benefit and risk of drug use in a population.

Some pioneering studies on prescribing patterns were conducted already in the 1950s. In the United Kingdom, initial studies were conducted by the National Health Service (NHS) to control prescribing and describe the influences on prescribing and prescribers as a social phenomenon [18]. The first international Drug Utilization studies focused on assessing differences in drug utilization between countries or regions [19–21]. Other studies focused on factors influencing the prescribing patterns of physicians [22–24]. In 1969, the WHO organized its first meeting on «Drug consumption» in Oslo. During the symposium, the researchers expressed the need for a common classification system for drugs as well as a technical unit of comparison in drug utilization studies [20]. To overcome this difficulty, 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, subsequently renamed defined daily dose (DDD) [21, 25, 26]. In 1975 the Norwegian Agency (Norsk Medisinaldepot) published a list of defined daily doses of drugs registered in Norway and classified according to a new classification system called the Anatomical Therapeutic Chemical (ATC) classification. The new classification was developed on the same basic principles as the classification of the European Pharmaceutical Market Research Association (EPhMRA) code, albeit extended to the substance level. The development of the ATC classification system and the DDDs enabled cross-national comparisons of drug utilization and was key to the future development of the discipline [26].

The small group of scientists active in these areas established the informal Drug Utilisation Research Group (DURG) in 1976. A seminal WHO publication Studies in Drug Utilization: Methods and application was published where the authors were all members of the original DURG group [21]. Due to close collaboration to WHO, the WHO Regional Office for Europe served as its secretariat, and this group was referred to as WHO-DURG for about 20 years. From 1993, the relationship between DURG and WHO loosened as the latter was unable to further support the DURG with secretarial functions. Therefore, in 1994, an independent European Drug Utilisation Research Group (EuroDURG) interim committee was elected; in 1996, at a meeting at Lake Balaton, Hungary, the EuroDURG was formally established [27, 28]. 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 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 were suggested [17, 29] as illustrated in Box 1.1.

Box 1.1 Aspects and consequences of drug utilization to be explored. From Dukes 1993 [17].

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 (non-compliance, 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.