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INTRODUCTION OF NEW MEDICINES IN SWEDEN

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Introduction of New Medicines in Sweden

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Payers and providers face challenges in enabling appropriate and sustainable access to new medicines. To help enable rational use of new medicines various policy options exist. In Sweden, horizon scanning, forecasting, value-based pricing and reimbursement, treatment recommendations, and assessment of drug utilization patterns and patient outcomes in routine clinical practice have been used to facilitate rational introduction of new medicines. Such activities, however, should be informed by research and be subject to continuous evaluation.

This thesis aims to examine selected elements of the process for managed introduction of new medicines. Study I provides an evaluation of the Swedish Horizon Scanning System. Study II assesses the impact of treatment recommendations on the use of new medicines in the specialized care setting. Finally, studies III and IV explore the utility of healthcare databases in the assessment of real-world use and outcomes of two specialist medicines prioritized for managed introduction.

Different types of data were used in these studies, including public assessment reports published by the European Medicines Agency, early assessment reports prepared by the Swedish Horizon Scanning System, national sales data on all inpatient and outpatient medicines, regional administrative healthcare services data, and national registers of Statistics Sweden and the National Board of Health and Welfare.

The evaluation of the Swedish Horizon Scanning System demonstrates that all innovative medicines that had substantial economic impact were identified and assessed prior to their introduction. The assessment of the impact of treatment recommendations shows that both local and regional treatment recommendations were associated with changes in the use of new medicines. Both regional and national healthcare databases provide the opportunity to study the use and outcomes of new medicines in routine clinical practice.

The findings indicate that healthcare decision makers can rely on the outputs of the Swedish Horizon Scanning System to keep informed of new medicines. Moreover, treatment recommendations appear to influence the uptake and utilization of new specialist medicines. Finally, even though the existing Swedish data sources provide unique research opportunities, the assessment of appropriate use and relevant outcomes of the growing number of new specialist medicines may still be impeded by a lack of fit-for-purpose data.

LIST OF SCIENTIFIC PAPERS

I Eriksson I, von Euler M, Malmström RE, Godman B, Wettermark B (2019) Did We See It Coming? An Evaluation of the Swedish Early Awareness and Alert System. Applied Health Economics and Health Policy 17:93–101

II Eriksson I, Komen J, Piehl F, Malmström RE, Wettermark B, von Euler M (2018) The Changing Multiple Sclerosis Treatment Landscape: Impact of New Drugs and Treatment Recommendations. European Journal of Clinical Pharmacology 74:663–70

III Eriksson I, Cars T, Piehl F, Malmström RE, Wettermark B, von Euler M (2018) Persistence with Dimethyl Fumarate in Relapsing-Remitting Multiple Sclerosis: a Population-Based Cohort Study. European Journal of Clinical Pharmacology 74:219–26

IV Eriksson I, Wettermark B, Bergfeldt K (2018) Real-World Use and Outcomes of Olaparib: a Population-Based Cohort Study. Targeted Oncology 13:725–33

CONTENTS

LIST OF ABBREVIATIONS

EMA European Medicines Agency

FDA Food and Drug Administration

RWD Real-world data

RWE Real-world evidence

TLV Dental and Pharmaceutical Benefits Agency

1 INTRODUCTION

This introductory chapter provides an overview of the development and approval of new medicines. This chapter also describes activities conducted by government agencies, payers, and providers that aim to facilitate access to new medicines and inform decision making around pricing, reimbursement, and formulary placement.

1.1 DRUG DEVELOPMENT

The introduction of a new medicine is a complex process spanning years and involving coordinated action of many stakeholders united by the common goal of improving patient outcomes. Drug development is filled with uncertainty and only few candidate molecules make it to the market and, of those that do, even fewer represent a significant breakthrough in medicine [1–5].

Transforming a candidate molecule to a pharmaceutical product requires extensive testing comprising nonclinical research and clinical trials [6]. Nonclinical research involves a variety of experiments to obtain information on safety (e.g. pharmacokinetics and toxicology studies) and efficacy (e.g. pharmacodynamics studies), as well as dosage, route, and frequency of administration [7–9]. When sufficient data from nonclinical studies have been obtained, permission to start clinical trials in humans is sought (approvals by both regulatory authorities and ethics committees are usually required) [10]. The aim of clinical trials is to examine the safety and efficacy of a candidate molecule in human volunteers.

There are four phases of clinical trials. Phase I trials are the first studies of the candidate molecule in humans, with a focus on clinical pharmacology [10]. These studies assess safety, determine the dosage range, identify side effects, and detect early evidence of efficacy if the candidate molecule is studied in patients with disease [10–12]. Phase II trials are exploratory efficacy studies that assess use for the targeted indication. These studies help determine dosage and inform the study design and selection of endpoints for use in subsequent clinical trials [6, 11, 13, 14]. Phase III trials are confirmatory studies designed to inform the benefit–risk assessment in support of marketing authorization [6]. Finally, Phase IV trials are conducted on marketed medicines to provide additional information on safety and efficacy [15].

To make a new medicine available to patients globally the pharmaceutical company must submit applications for product registration to regulatory authorities such as the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). Marketing authorization is granted if the new medicine fulfills established quality, safety, and efficacy criteria and has a positive benefit–risk balance. Generally, Phase III trials are expected to have been completed at the time of submission of the marketing authorization application, but a new medicine can also be approved based on results from Phase II trials [16–20]. After approval, new research on the medicine can be initiated to study if it can be used for other indications, be administered via other administration routes, or be combined with other medicines.

Following regulatory approvals new medicines will be made available for use across markets. In line with the scope of this thesis the remainder of this chapter will cover key aspects related to the introduction of new medicines in Sweden.

1.2 REGULATORY APPROVAL

In Sweden, generally, there are four distinct registration pathways available for applying for marketing authorization: national procedure, mutual recognition procedure, decentralized procedure, and centralized procedure [21]. A brief summary of these is provided below. Detailed and up-to-date information can be found on the websites of EMA and the Swedish Medical Products Agency [21, 22].

If a medicine is intended for marketing only in Sweden, the pharmaceutical company can submit a marketing authorization application to the Swedish Medical Products Agency (the national procedure) [21]. The mutual recognition procedure allows the marketing authorization granted in one member state to be recognized in other European Union countries. In the decentralized procedure, a medicine that has not yet been authorized in the European Union can be authorized in more than one member state in parallel. In practice, the national, mutual recognition, and decentralized procedures are seldom used when marketing authorization is sought for a new innovative medicine.

The centralized procedure allows pharmaceutical companies to submit a single marketing authorization application to EMA. If authorized, the medicine can be marketed throughout the European Union [22]. The centralized authorization procedure is compulsory for new medicines with specific therapeutic indications (human immunodeficiency virus or acquired immune deficiency syndrome, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune diseases, viral diseases). Moreover, biotechnology-derived medicines, advanced therapy medicines, and orphan medicines must also be authorized through the centralized procedure. The procedure may also be used if the applicant can show that the medicinal product constitutes an important therapeutic, scientific, or technological innovation. For a submitted marketing authorization application, EMA publishes either a European public assessment report that describes the scientific basis for its recommendation or, if the application was withdrawn, the withdrawal letter together with a withdrawal assessment report.

Regulatory agencies, including EMA, have aimed at fostering development of medicines with the potential to address unmet medical needs and at facilitating faster access for patients to innovative medicines [22–25]. Existing regulatory tools include scientific advice, accelerated assessment, conditional marketing authorization (approval based on limited clinical data with provision of comprehensive data within an agreed timeframe), and compassionate use (use of unauthorized medicines outside the clinical study setting). Recent initiatives include the launch of the priority medicines scheme based on enhanced interaction and early dialogue with developers of promising medicines in order to optimize development plans and speed up evaluation [22].

1.3 PRICING AND REIMBURSEMENT

On the path toward commercialization of a new medicine, the demonstration of a positive benefit–risk balance is only one step. Increasingly, pharmaceutical companies also have to demonstrate value for money to ensure reimbursement by payers.

Sweden has a national healthcare system that is primarily funded through direct taxation [26, 27]. Health policy is governed at the national level, while regions are largely responsible for decision making and provision of healthcare services. The Dental and Pharmaceutical Benefits Agency (TLV)—a national government agency—is responsible for value-based pricing and reimbursement of outpatient prescription medicines [28]. Medicines used in hospitals are not covered by the national reimbursement scheme. While the TLV can be asked to assess the cost-effectiveness of some new medicines intended for hospital use, the procurement of all inpatient medicines is managed by the regions.

For an outpatient medicine to be reimbursed and included in the national pharmaceutical benefits scheme the pharmaceutical company needs to submit an application to the TLV [28]. In the application the company states the price applied for and provides supporting clinical and health economic documentation. The decision of the TLV is based on a number of factors, including three fundamental principles—human value, need and solidarity, and cost-effectiveness—that guide priority setting in the healthcare system (the Health and Medical Services Act [SFS 2017:30]). Provided that the first two guiding principles are fulfilled, reimbursement is granted if the TLV finds that the requested price is justified in relation to the value the new medicine brings. This value-based approach to pricing and reimbursement aims to provide access to cost-effective and innovative medicines and to ensure cost-effective use throughout the product's lifecycle.

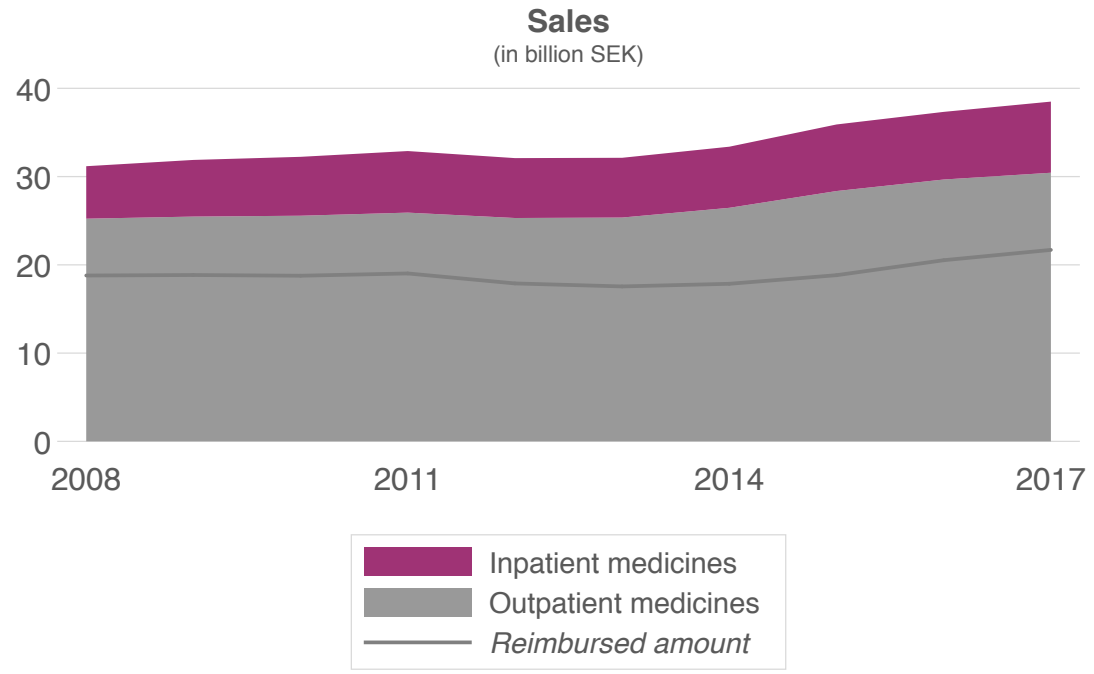
There are two main types of reimbursement that the TLV may grant [28]. General reimbursement means that a medicine is eligible for reimbursement for its entire approved indication. Reimbursement may also be restricted to a certain area of use or a subgroup of patients. Additionally, conditions for reimbursement may apply, such as the requirement that the pharmaceutical company provides follow-up data on the use and outcomes of the approved medicine. Also, within the framework of the pricing and reimbursement scheme, a pharmaceutical company and the regions may enter into an agreement that in turn impacts the decision by the TLV. In practice, such a managed entry agreement can mean that the list price set by the TLV does not apply (e.g. by way of a price discount or risk sharing arrangement).

Detailed and up-to-date information on the pricing and reimbursement of medicines in Sweden can be found on the TLV website [28]. Moreover, a comprehensive overview of the Swedish healthcare system with focus on pricing and reimbursement of medicinal products has recently been published [29].

1.4 FINANCING OF NEW MEDICINES

While the TLV decides on which medicines are included in the national pharmaceutical reimbursement scheme, the agency does not hold budget responsibility. As mentioned earlier, the regions are largely responsible for decision making and provision of healthcare services, including financing of outpatient and inpatient medicines. Healthcare services are financed by local taxes and supplemented by central government grants and patient copayments [26].

Costs of inpatient medicines are covered in full by the regions. For reimbursed outpatient medicines the regions receive a designated government grant and patients are charged a copayment (up to SEK 2300 for a rolling 12-month period). Patients pay the full amount for prescription medicines that are not included in the reimbursement scheme as well as for over-the-counter medicines [28].



Inpatient medicines = 'rekvisitionsförsäljning'

Source: Swedish eHealth Agency (annual data)

Figure 1. National sales of medicines (excluding over-the-counter medicines)

In Sweden, annual sales of inpatient and prescribed outpatient medicines amount to almost SEK 40 billion, of which SEK 30 billion is for prescribed outpatient medicines (Figure 1). The introduction of new medicines for the treatment of hepatitis C and cancer as well as the growing use of some older products, such as non-vitamin K antagonist oral anticoagulants, have contributed to the increase in pharmaceutical expenditure seen in recent years.

1.5 CHALLENGES PAYERS FACE IN ENABLING ACCESS TO NEW MEDICINES

The value that new innovative medicines bring is well recognized and efforts are made to encourage pharmaceutical innovation to address unmet needs [22, 30]. However, not all new medicines are breakthroughs, yet many come with a price premium, and it is not always easy to discern the value at the time of introduction. This is particularly true for medicines approved based on limited data [31, 32]. Even if an extensive clinical development program has been completed, at the time of introduction there is always uncertainty about real-world effectiveness, safety, and economic impact. Moreover, as the number of treatment options in a given therapeutic area increases it can become more difficult for patients and clinicians to select the most optimal treatment. Comparative effectiveness and safety data—not only in relation to the established standard of care but also among recently introduced treatment options—are thus needed to inform decision making. Finally, even if a new medicine is indeed a breakthrough, the question of affordability inevitably comes up [33–36].

It is acknowledged that payers face various challenges in enabling rational use of new medicines [37–41] and the subject of access has increasingly been discussed in recent years [42–45]. The past decades have seen a rapid increase in the number of new specialist medicines, including novel approaches to treat cancer and rare diseases as well as cures such as new medicines for hepatitis C, that address previously unmet needs. In parallel with scientific advances that fuel the research and development pipeline, patients are also changing. Patients are becoming more informed, engaged, and empowered and healthcare systems are moving toward person-centered care [46–48]. Also, demographic changes are contributing to the growing burden of chronic diseases [49, 50]. These parallel developments, however, unfold in the reality of constrained healthcare budgets.

1.6 EVOLUTION OF THE MANAGED INTRODUCTION OF NEW MEDICINES IN SWEDEN

In 2005, following years of rapid growth in pharmaceutical expenditure, an initiative was launched by the drug and therapeutics committee in Region Stockholm with the aim to develop an effective model for the introduction of new medicines [37, 51]. In addition to the growing budget impact, uncertainty around patient outcomes was a key driver of the initiative [37]. The focus was on specialist medicines and medicines intended for use in large patient populations [51]. The resulting model comprised a number of activities, including horizon scanning and forecasting with the aim to inform and allow healthcare providers and administrators to prepare for the introduction of new medicines. For selected medicines, regulatory data and published clinical trials were used to assess the clinical value in relation to established treatment options. For medicines evaluated by the TLV, potential health economic consequences were also assessed. For medicines selected for managed introduction, treatment recommendations were developed and requirements for the assessment of

use and outcomes in routine clinical practice were defined. This model for managed introduction and rational use of new medicines was facilitated by the involvement of medical experts and prescribers. Furthermore, various communication tools and educational efforts were used to facilitate the rational use of new medicines. In 2008, a comprehensive description of the model was published in the Swedish medical journal Läkartidningen [51].

The regional model described above served as the foundation upon which further processes for managed introduction and assessment of new medicines were developed [39, 52, 53]. As part of the National Pharmaceutical Strategy introduced in 2011, the Swedish Association of Local Authorities and Regions established a national collaboration to promote effective, safe, and equitable use of new medicines [54]. This collaboration has brought together the regions, drug and therapeutics committees, government agencies, and pharmaceutical companies. An up-to-date description of the national model can be found on a dedicated website [55].

1.7 HORIZON SCANNING

As mentioned earlier, horizon scanning was included as a step in the Stockholm model to support planning and to optimize the readiness of the healthcare system for the introduction of new medicines [51, 53]. Horizon scanning can be defined as the "systematic identification of health technologies that are new, emerging, or becoming obsolete and that have the potential to effect health, health services, and society" [56]. An in-depth description of the evolution and current status of horizon scanning in Sweden was published as part of this thesis project (see Appendix).

Over the years, horizon scanning has become a key early health technology assessment tool [42]. In light of this, it is becoming increasingly important to critically assess horizon scanning outputs. In Sweden, both regional and national decision makers rely on the Swedish Horizon Scanning System to keep informed and prepare for the introduction of new medicines [53]. The prioritization by the Horizon Scanning Working Group may, for example, inform the priority setting at the regional level. Moreover, at the national level, it can influence the decision to include a medicine in the national process for managed introduction [55]. Therefore, it is critical that prioritization decisions are made judiciously and are as accurate as possible.

1.8 TREATMENT RECOMMENDATIONS

Treatment guidelines and recommendations—that can be defined as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances" [57]—have the potential to improve quality of care, optimize patient outcomes, and reduce costs by focusing resources on the most effective treatment options [58]. Additionally, they can serve as a foundation for performance measures, appropriate use criteria, and clinical decision support tools. For decades, various stakeholders, including government agencies, physician organizations, academic and independent research centers, payers, and hospitals, have

issued treatment guidelines and recommendations to facilitate the rational use of medicines.

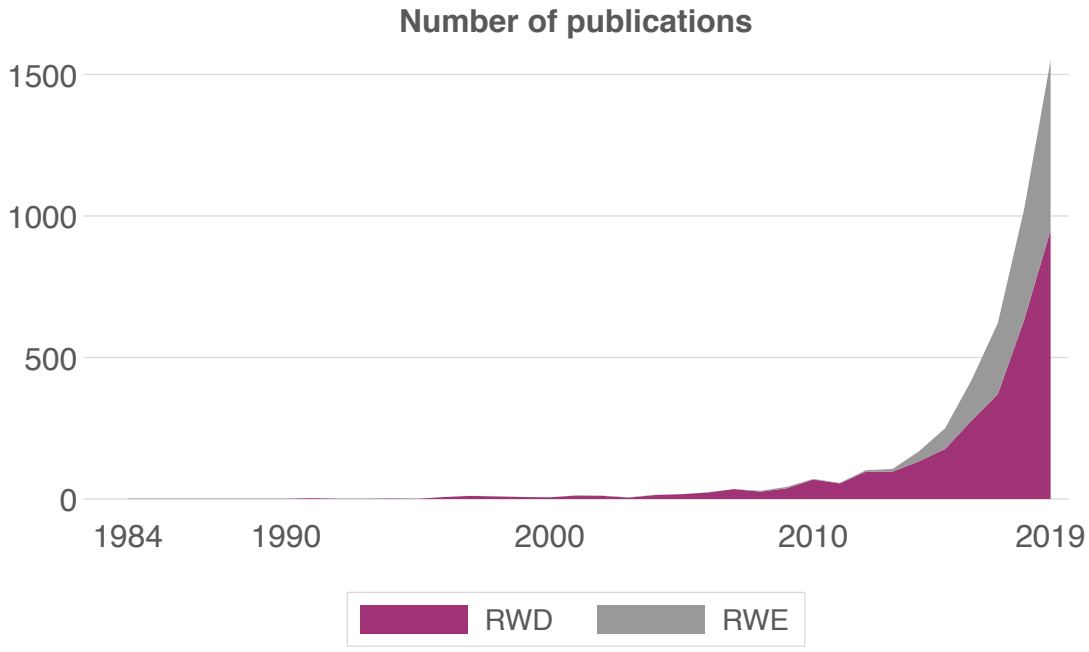
In Sweden, recommendations on the use of medicines have been primarily developed by drug and therapeutics committees. The first drug and therapeutics committee was established in 1961 at the Karolinska University Hospital in Stockholm with the aim to evaluate new and established medicines and define the hospital formulary [59]. Over the years similar functions were established across Sweden and in 1997 it became mandatory for each region to operate a regional drug and therapeutics committee [60, 61]. This was followed by the devolution of responsibility for the financing of medicines from the state to the regions [62].

The aim of the regional drug and therapeutics committees is to develop locally relevant treatment recommendations and formularies to support both general practitioners and specialists [52]. The work is organized around expert groups on therapeutic areas. As an example, the drug and therapeutics committee in Region Stockholm aims to operate a transparent process for developing recommendations, which involves experts and clinicians (using strict criteria for handling potential conflicts of interest), prescribing feedback and decision support, continuous medical education, and a model that links financial incentives to the level of adherence to the recommendations [63]. The committee manages an essential medicines formulary (the Wise List) that has successfully been used to influence prescribing behavior [63–68].

Additionally, a number of Swedish government agencies are involved in supporting healthcare decision makers. For example, the National Board of Health and Welfare issues national guidelines to support decisions concerning patient care and the allocation of resources within healthcare and social services [69]. Also, as part of the national process for managed introduction of new medicines, the New Therapies Council issues recommendations on the use of new medicines with the aim to enable effective, safe, and equitable treatment of patients across regions [53, 70].

1.9 REAL-WORLD DATA AND REAL-WORLD EVIDENCE

Over the past decades, observational research has provided evidence on the use, benefits, and harms of medicines [71]. Substantial methodological advances have been made and greater knowledge of the potential and limitations of various types of data has been acquired. Technological developments have enabled collection of unprecedented amounts of data as part of healthcare provision. The terminology used has also evolved with the terms "real-world data" and "real-world evidence" rapidly becoming dominant (Figure 2).



RWD real-world data *RWE* real-world evidence

Source: ncbi.nlm.nih.gov/pubmed (annual data)
Data as of August 2019, extrapolated until the end of the year

Figure 2. Number of hits for "real-world data" and "real-world evidence"

Multiple definitions of "real-world data" (RWD) and "real-world evidence" (RWE) have been proposed [72, 73]. The United States FDA—in a report outlining the agency's planned framework for use of RWE to support regulatory decisions—provides the following definitions [74]: "[RWD] are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources" and "[RWE] is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."

While many have defined RWD as data collected in non-randomized controlled trial settings [73], others stress that "real-world research and the concepts of a planned intervention and randomization are entirely compatible" [72]. The term RWE can thus apply to a broad range of research that encompasses both observational studies and studies that incorporate planned interventions regardless of whether treatment is allocated through randomization or not. In view of this, RWE is evidence that is derived from analyses of data from multiple sources outside conventional clinical research settings [72].

Sources of RWD include electronic health records, administrative healthcare data, patient registries, and patient-generated data. A thorough description of commonly used RWD sources, including related topics such as data quality and record linkage can be found elsewhere [75]. Sweden has a considerable number of administrative and medical registers that cover the entire population [76]. These registers provide unique possibilities for research as they allow for continuous follow-up and individual-level

linkage of records between national socioeconomic registers, up-to-date death records, data generated within the healthcare system, biobanks, and population-based surveys.

RWE has become a multidisciplinary field that brings together the established disciplines of drug utilization research, health economics and outcomes research, and pharmacoepidemiology [77]. The ultimate goal of RWE generation is to support decision making by stakeholders in the healthcare system. Use cases include regulatory approval [78–81], pricing and reimbursement [82–84], formulary decisions [85–88], as well as continued benefit–risk assessment of marketed medicines [89, 90].

However, the evaluation of medicines outside of controlled clinical research settings is fraught with methodological challenges [91]. Concerns have also been raised that there is shortage of qualified researchers and that current educational efforts are inadequate [92]. These concerns are further compounded by the growing availability of user-friendly analytics tools that inadvertently may lead to an increased number of poorly designed and executed studies [72]. Nonetheless, well-executed and timely analyses can play an important role in healthcare decision making.

2 AIMS

This thesis aims to examine the process for managed introduction of new medicines in Sweden. Study I provides an evaluation of the Swedish Horizon Scanning System. Study II assesses the impact of treatment recommendations on the use of new medicines in the specialized care setting. Studies III and IV explore the utility of healthcare databases in the assessment of real-world use and outcomes of two specialist medicines prioritized for managed introduction. The objectives of the four studies of this thesis are presented below.

Study I To assess whether the Swedish Horizon Scanning System identified and accurately prioritized new medicines.

Study II To assess the impact of treatment recommendations on the utilization of disease-modifying treatments in relapsing-remitting multiple sclerosis.

Study III To describe patients initiating dimethyl fumarate and measure treatment persistence in treatment-naïve patients and in patients switching to dimethyl fumarate from other disease-modifying treatments.

Study IV To describe the use of olaparib and measure time to treatment discontinuation and overall survival in patients treated during the first three years following regulatory approval.

3 METHODS

This chapter provides an overview of data sources, study designs, and statistical analyses used in the four studies that form the basis for this thesis. Table 1 presents an overview of the studies. The chapter concludes with a discussion around ethical issues that were considered during the course of the research.

Table 1. Overview of the studies that form the basis for this thesis

	Description	Design	Data sources	Study period
Study I	Evaluation of the Swedish Horizon Scanning System (Early Awareness and Alert System)	Diagnostic accuracy study	European Medicines Agency: European public assessment reports; data on withdrawals of initial marketing authorization applications Swedish eHealth Agency: national sales data Horizon Scanning Working Group: early assessment reports	2010–2017
Study II	Assessment of the impact of both the introduction of new medicines and treatment recommendations on multiple sclerosis drug utilization	Interrupted time series study	Region Stockholm: administrative healthcare services data	2011–2017
Study III	Description of patients treated with dimethyl fumarate and assessment of treatment outcomes using regional data	Cohort study	Region Stockholm: administrative healthcare services data	2010–2017
Study IV	Description of patients treated with olaparib and assessment of treatment outcomes using national data	Cohort study	Statistics Sweden: Total Population Register National Board of Health and Welfare: National Patient Register; Prescribed Drug Register; Cancer Register; Causes of Death Register Swedish eHealth Agency: national sales data	2005–2017

3.1 DATA SOURCES

This section provides an overview of the data sources used in the studies.

Study I

Data for the study on the Swedish Horizon Scanning System were collected from EMA, the Swedish eHealth Agency, and the Horizon Scanning Working Group.

First, public information on initial marketing authorization applications was obtained from EMA for all medicinal products processed between 1 January 2010 and 31 December 2015. All European public assessment reports on medicines and all withdrawals of initial marketing authorization applications were compiled.

Second, national aggregate monthly sales data for all new medicines were obtained from the Swedish eHealth Agency. This is an agency tasked to lead and coordinate national government eHealth initiatives [93]. As part of its remit, the agency maintains national records of all pharmaceutical sales by pharmacies, retailers, and wholesalers—covering both hospital sales and medicines dispensed in outpatient care. For each transaction, information is captured on the medicinal product's formulation, strength, and pack size, as well as price and the date of sale.

Finally, all medicines prioritized by the Swedish Horizon Scanning System were identified and all early assessment reports were retrieved from the Horizon Scanning Working Group.

Studies II and III

The two studies on regional drug utilization and treatment outcomes in multiple sclerosis used data derived from the VAL data warehouse owned and operated by Region Stockholm [94]. One of the key responsibilities of Region Stockholm is the provision of healthcare to all residents of the region. The VAL data warehouse contains data on all provided healthcare services. Region Stockholm—with 12.5 million primary care visits, 5.5 million outpatient specialist visits, and 260,000 hospital admissions in 2018 [95]—is one of the largest healthcare providers in Europe [96].

In an international context, the VAL data warehouse is unique in providing years of longitudinal data that facilitate comprehensive follow-up capabilities of all care encounters that patients have across the entire healthcare system [97]. Consequently, the VAL data are of value for resource planning as well as quality and effectiveness evaluations of healthcare providers. The content of the VAL data warehouse databases ranges from detailed information on primary care visits and dispensed medicines to migration dates to and from the region. All healthcare providers that are contracted by Region Stockholm regularly submit information and the databases are generally updated on a monthly basis.

All data on patient care encounters—inpatient, outpatient specialist, and primary care—were retrieved from databases that contain information on providers, diagnoses,

and procedures. Outpatient drug utilization records were obtained from the pharmacy dispensing database. Hospital-administered medicines were derived using procedure codes recorded during hospitalizations and outpatient specialist care visits. Patient characteristics, migration dates, and mortality data were also obtained.

Study IV

The national study on olaparib was conducted using data from the Swedish population-based registers. These registers are managed by Statistics Sweden and the National Board of Health and Welfare.

Statistics Sweden is a government agency responsible for developing, producing, and disseminating official statistics [98]. The agency maintains a number of registers and databases that are often used in research, such as the Total Population Register that provides the foundation for the nation's population and household statistics [99]. Examples of information recorded in this register include sex, age, marital status, migration, births, deaths, marriages, and divorces.

The National Board of Health and Welfare is a government agency under the Ministry of Health and Social Affairs with a number of responsibilities related to health and social care, including the development of national care support programs, the development of regulations and guidelines, and the evaluation of quality and effectiveness of healthcare providers [69]. As a part of its remit, the National Board of Health and Welfare develops and maintains a number of nation-wide registers that cover health data and social services.

For the study, individual-level register data were provided by the agencies described above. Deterministic linkage between records [100] was facilitated by matching on the personal identity number, which is assigned to all Swedish residents.

Medical information was obtained from the National Patient Register, which contains all inpatient care and outpatient visits, in addition to day surgery and psychiatric care from both private and public healthcare providers in Sweden [69]. Broadly, the register contains four types of data: patient data (e.g. sex, age, and place of residence), healthcare provider data, administrative data (e.g. date of stay and type of care), and medical data in terms of recorded diagnoses and procedures.

The Prescribed Drug Register provided data on all dispensed prescription medicines in ambulatory care [101]. This register contains records of all medicines dispensed in outpatient pharmacies with details on the patient and the prescriber, the medicine name, anatomical therapeutic chemical classification system (ATC) code, strength and pack size, prescribing and dispensation dates, and costs (reimbursed expenditure and patient copayment).

Healthcare providers in Sweden are mandated to report newly detected cancer cases to the Swedish Cancer Register [102]. Each new cancer case—whether diagnosed through clinical, morphological, or laboratory findings, including cases diagnosed at

autopsy—generates a report. Recorded medical data include site of tumor, histological type, and stage. For this study, information was obtained on the primary site of the tumor, its malignancy, histology, stage, and the date of diagnosis.

In addition, mortality data were derived from the Causes of Death Register, which is the source of official mortality data in Sweden [103].

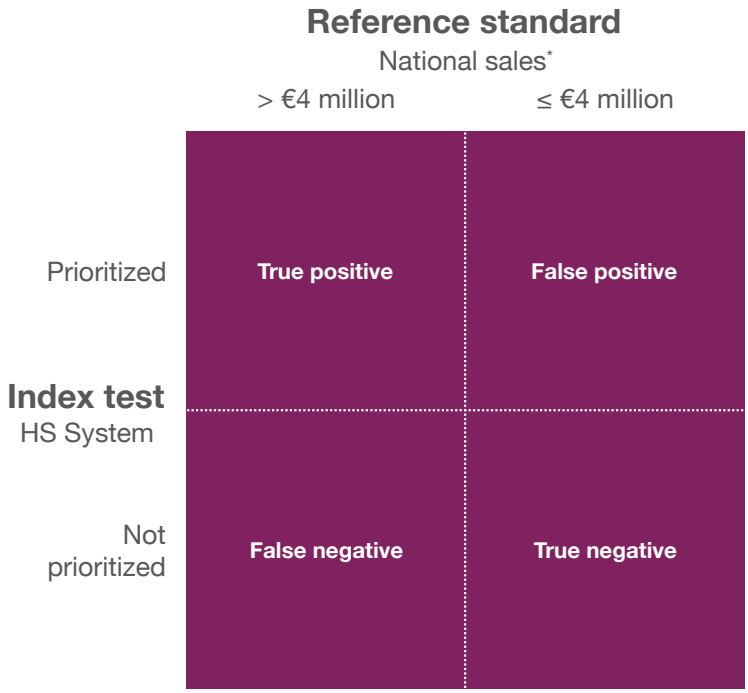
Finally, the Swedish eHealth Agency provided aggregate monthly sales data that were used to estimate use of medicines not captured at the individual level, such as medicines administered in the hospital setting [93].

3.2 STUDY DESIGNS

This section describes the diagnostic accuracy, interrupted time series, and cohort study designs used in this thesis.

Study I

Methodology commonly used in diagnostic accuracy studies was used to evaluate the Swedish Horizon Scanning System. In the assessment of the discriminative power of a test, the index test's classification of a target condition is compared with the classification of a reference standard [104, 105]. In the context of this study, the prioritization made by the Swedish Horizon Scanning System comprised the index test, while national sales data served as the reference standard (Figure 3).



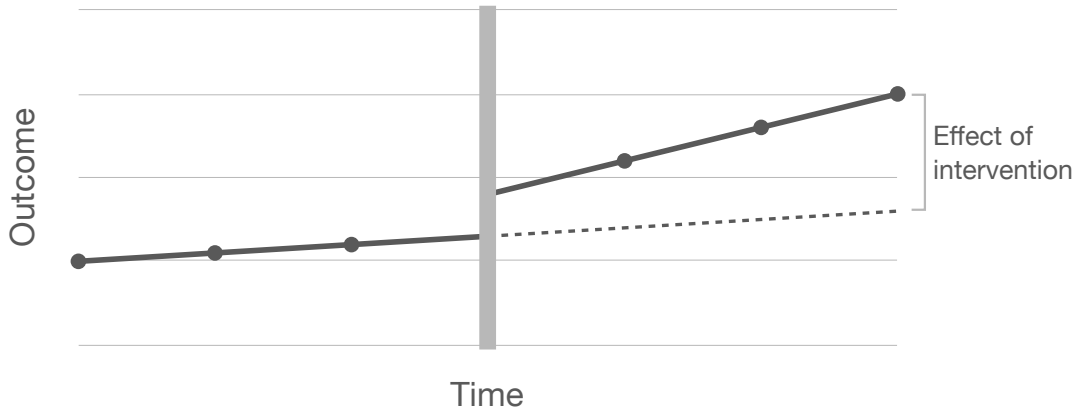
HS horizon scanning
* In the second year on the market

Figure 3. Contingency table describing the relationship between results of the index test and the reference standard

All initial marketing authorization applications for medicinal products processed by EMA between 1 January 2010 and 31 December 2015 comprised the study population and were classified using the index test and the reference standard. Sensitivity was defined as the proportion of prioritized medicines among all medicines exceeding the sales threshold (€4 million). Specificity was defined as the proportion of non-prioritized medicines among all medicines below the sales threshold. Positive predictive value was defined as the proportion of medicines exceeding the sales threshold among all prioritized medicines. Negative predictive value was defined as the proportion of medicines below the threshold among all non-prioritized medicines.

Study II

An interrupted time series design was used to assess the impact of treatment recommendations [106]. The outcome of interest was the number of users of each disease-modifying treatment before and after different types of interventions that were hypothesized to have had an impact on drug utilization. The study design is summarized in Figure 4.

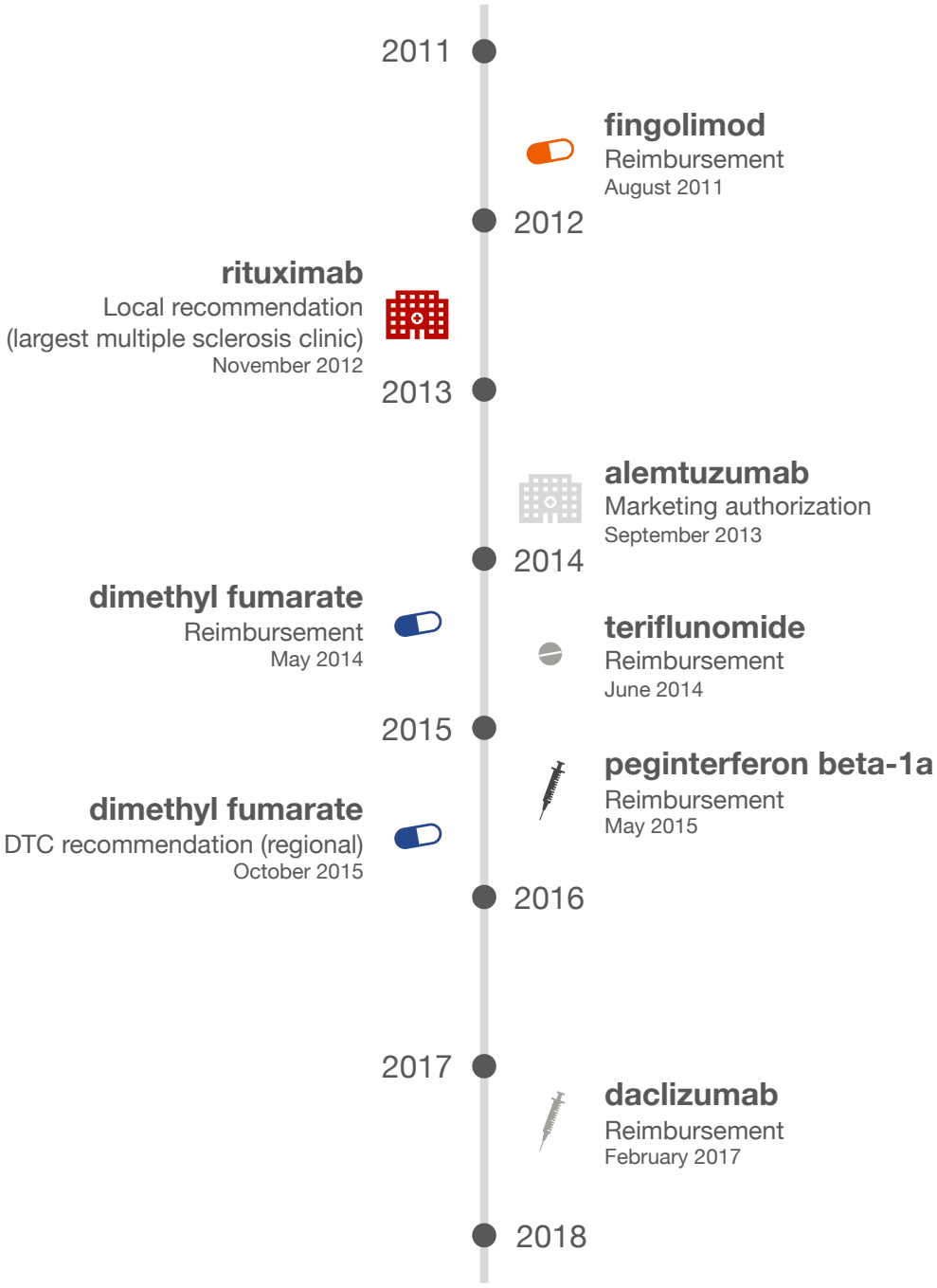


A time series of the outcome is used to establish a trend. Following the intervention, the outcome variable is observed for an immediate effect and a change in the trend compared to the predicted values. The time point of the intervention is indicated by the vertical bar.

Figure 4. Visualization of the interrupted time series study design

A population-based study of all Region Stockholm residents diagnosed with multiple sclerosis and treated with disease-modifying treatments was conducted. All patients with at least one diagnosis of multiple sclerosis and at least one dispensation or administration of a disease-modifying treatment from 1 January 2011 to 31 December 2017 comprised the study population.

Figure 5 depicts the introduction of new medicinal products and the dissemination of new treatment recommendations—referred to as interventions—that may have influenced the utilization of disease-modifying treatments in Region Stockholm.



DTC drug and therapeutics committee

Figure 5. Interventions that may have influenced the utilization of disease-modifying treatments in multiple sclerosis

Study III

A population-based cohort study was conducted to assess all Region Stockholm residents who initiated treatment with dimethyl fumarate (Tecfidera) from its regulatory approval until 31 May 2017. A graphical depiction of the study design is provided in Figure 6. Dimethyl fumarate persistence was defined as the number of days from the cohort entry date until either discontinuation or switching to another disease-modifying treatment.

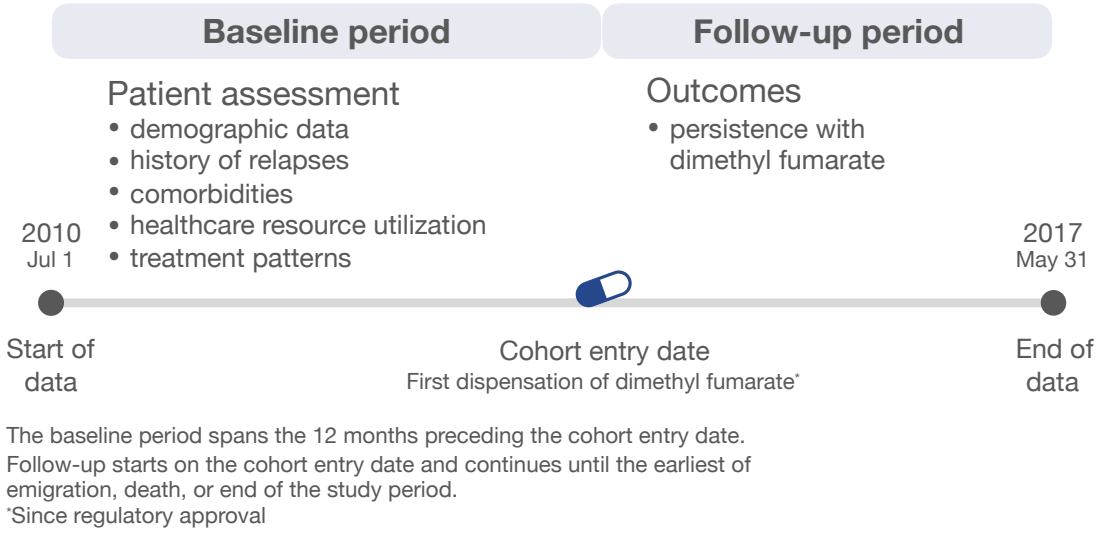


Figure 6. Cohort study schematic (Study III)

Study IV

A population-based cohort study was conducted to assess all residents of Sweden who initiated treatment with olaparib (Lynparza) from its regulatory approval until 31 December 2017. A graphical depiction of the study design is provided in Figure 7. Time to olaparib discontinuation was defined as time from the cohort entry date to the end of supply of dispensed olaparib or death. Overall survival was defined as time from the cohort entry date to the date of death from any cause.

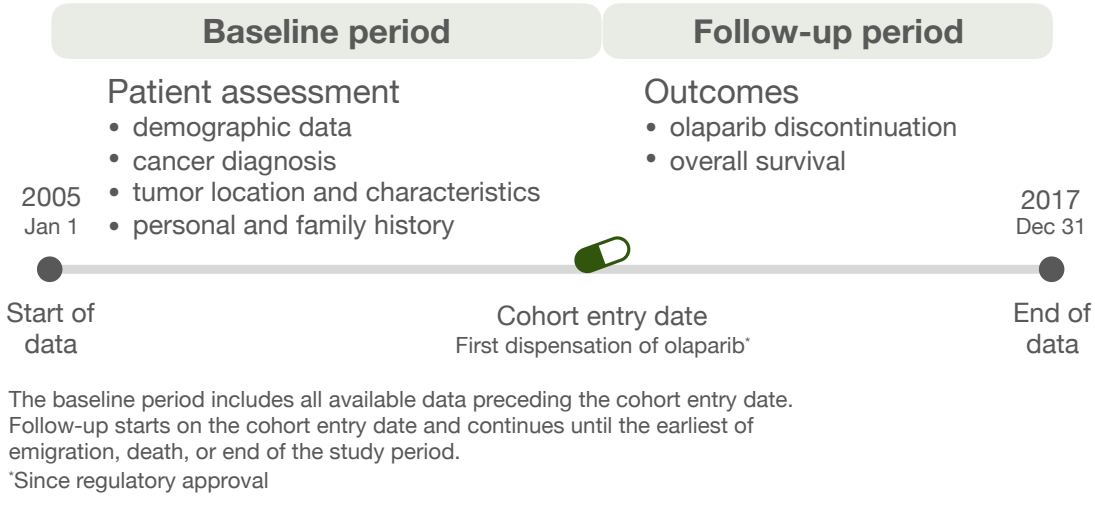


Figure 7. Cohort study schematic (Study IV)

3.3 STATISTICAL ANALYSES

Baseline characteristics of study populations were presented using descriptive statistics. Categorical data were described using frequencies and proportions. For continuous data, means or medians were presented together with standard deviations or ranges.

Study I

The accuracy of the prioritization of the Swedish Horizon Scanning System was summarized in a contingency table. Outcome statistics were reported as sensitivity, specificity, positive predictive value, and negative predictive value with 95% Clopper–Pearson binomial confidence intervals [107, 108].

Study II

To determine whether the identified interventions could have had the potential to influence utilization patterns of disease-modifying treatments, the number of monthly prevalent users of each medicine was plotted. A linear regression model was fitted over each time series for visual inspection of time trends. With the Durbin–Watson statistic, data were tested for first-order autocorrelation and, if present, corrected for this with an autoregressive term in the model [109, 110].

A segmented regression model with a step function was used to perform the interrupted time series analysis [106, 111]. Two different outcomes—the step change (immediate effect) and the change in slope (trend)—were both compared to the predicted values. Pre- and post-intervention timeframes were chosen so that none of the other interventions overlapped with these time periods. When the step change clearly lasted longer than one month, the model was shaped to this.

Studies III and IV

The main treatment-related outcomes were treatment persistence (Study III) and time to discontinuation and overall survival (Study IV). These time-to-event endpoints were analyzed by deriving nonparametric estimates of the survivor functions [112].

In all analyses, the duration variable for each subject was defined as the time from treatment initiation (cohort entry date) to the outcome of interest (event), loss to follow-up, or end of study, whichever came first. Subjects who did not have the event of interest during the follow-up period were censored. The Kaplan–Meier product-limit method was used to derive survival estimates and to plot the survivor function.

Statistical software

Data management and analyses in Study I were conducted using Stata 14.2 (College Station, TX, United States). For Study II, data management was conducted using SAS 9.4 (Cary, NC, United States) and analyses were conducted using Stata 14.2 and IBM SPSS Statistics 24.0 (Armonk, NY, United States). Data management and analyses in studies III and IV were conducted using SAS 9.4.

3.4 ETHICAL CONSIDERATIONS

A number of ethical issues were considered for the studies of this thesis.

Publicly available data related to marketing authorization applications submitted to EMA as well as aggregate-level national sales data were used in Study I. This research did not involve humans and was therefore exempt from ethics review requirements. Studies II, III, and IV, however, were observational studies based on individual-level data. Because such data contain sensitive personal information, ethics committee review was required [113]. In Sweden during the conduct of these studies a number of regulations governed ethical vetting of research that involves humans (the Ethical Review Act [SFS 2003: 460] and the statutes SFS 2003:615, SFS 2007:1069, and SFS 2007:1068). Information on ethics approvals obtained for this thesis is provided in Table 2.

Table 2. Ethics approvals obtained for each study

	Application type	Title	Date of decision	Reference
Studies II and III	Original submission	Assessment of new medicines for treatment of multiple sclerosis: a database study [Uppföljning av nya läkemedel för behandling av multipel skleros: en registerstudie]	2016-02-17	2015/2329-31/4
Study IV	Original submission	Assessment of drug utilization in cancer care in the Stockholm–Gotland healthcare region [Registrering och uppföljning av läkemedelsbehandling inom cancervården i hälso- och sjukvårdsregionen Stockholm–Gotland]	2012-09-06	2012/1236-31/4
	Amendment		2012-10-29	2012/1726-32
	Amendment		2015-10-20	2015/1790-32

Specific items in the application for ethics approval that are relevant and important to observational research include privacy and confidentiality of data, security of data, informed consent, and risks and benefits of the research project.

Privacy refers to the right of individuals to keep information about themselves from being disclosed to others and to be free from surveillance or interference from other individuals, organizations, or the government [114]. Confidentiality addresses the issue of how personal data that have been collected may be held and used by the organization that collected the data, what other secondary uses may be made of the data, and when the permission of the individual is required for such uses [115]. Security can be defined as the procedural and technical measures required to prevent

unauthorized access, modification, use, and dissemination of data stored or processed in a computer system, to prevent any deliberate denial of service, and to protect the system in its entirety from physical harm [116].

Centralized de-identification of data provided protection of privacy and confidentiality within this research project. Region Stockholm performs de-identification before data are released to the VAL data warehouse. Similarly, Statistics Sweden and the National Board of Health and Welfare process national individual-level data before delivery to researchers. Moreover, the researchers themselves are bound by regulations and moral responsibility to use data only for purposes of the approved research.

De-identification also entails that researchers do not know who the research subjects are, which makes it impossible to seek informed consent from these individuals. The lack of informed consent can be viewed as an issue. However, the observational studies conducted within this research project had no impact on the care provided to patients, nor did the research require any contact with the study subjects. There is generally, both in Sweden and internationally, no requirement for informed consent when using only de-identified data from administrative databases. Moreover, seeking informed consent may even hamper research and make addressing objectives of observational studies unattainable [117].

In terms of data security, the environment in which research was conducted was tightly controlled. Access to data was restricted to authorized researchers only. Additionally, security of data was protected through procedural and technical measures including, but not limited to, firewalls, encryption, password access, and monitoring of users.

Finally, risks and benefits of the research project should also be discussed. The primary concern is the unlikely, but nonetheless possible, risk of breaching privacy and confidentiality of individuals included in research. It must be acknowledged that even the most elaborately de-identified datasets may retain identifiable information and concerns over current de-identification standards have been expressed [75]. In fact, the possibility to re-identify individuals from de-identified data has been demonstrated and it may be that it is no longer possible to create truly de-identified or anonymized datasets. Legislation, professional standards, and moral responsibility are thus of key importance and it is expected that regulations will continue to evolve in order to guarantee that released data are used strictly for the approved research.

For the studies of this thesis, routinely collected individual-level data can be considered the best source of information to address the study objectives. The research provided important information on the uptake and use of new medicines among all patients, including description of patient characteristics that can highlight possible gaps and unmet medical needs. The dissemination of information on patient outcomes in routine clinical practice can help patients, clinicians, payers, and policy makers to make informed decisions around the use of new medicines.

4 RESULTS

This chapter provides a summary of the results. For each study, the study population is described followed by key findings.

4.1 STUDY I

The output generated by the Swedish Horizon Scanning System, since its inception until the end of 2015, as well as sales of all new medicines introduced on the Swedish market were assessed.

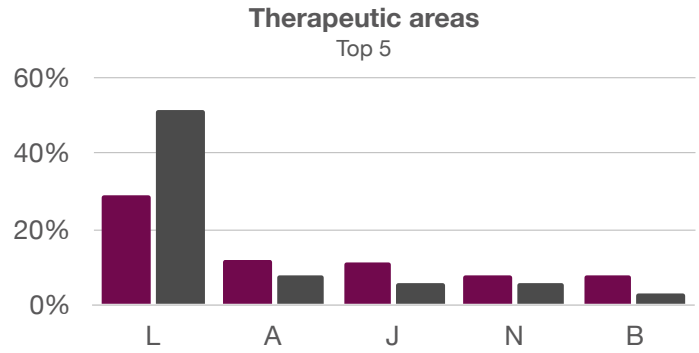
From 2010 to the end of 2015, EMA published 462 European public assessment reports on medicinal products that were either granted or refused marketing authorization. During the same time period, the initial marketing authorization applications for 64 additional medicinal products were withdrawn by the pharmaceutical companies. After applying the study selection criteria—primarily resulting in the exclusion of generics or known active substances for use in an already approved indication—253 medicinal products remained in the study population.

During the same time period, the Swedish Horizon Scanning System published early assessment reports for 104 new medicines. Following the exclusion of 33 reports—most frequently for covering extensions of indications—71 prioritized medicines remained (positive index test). Figure 8 provides information on the study population and the prioritized medicines.

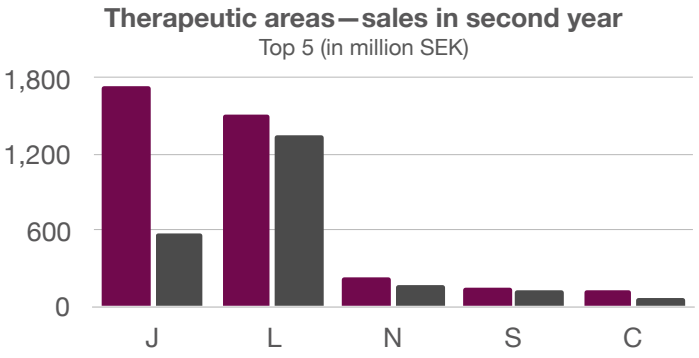
Table 3 lists all 71 prioritized medicines. Of these, 16 products were classified as having substantial economic impact on the healthcare system. An additional five medicinal products also had substantial sales but were not prioritized by the Swedish Horizon Scanning System (Table 4).

Among the prioritized medicines, 55 were classified as not having substantial economic impact. Seven of these medicines were not granted marketing authorization. An additional six medicines were authorized but had no sales in the first two years on the market (naltrexone/bupropion [Mysimba], teduglutide [Revestive], afamelanotide [Scenesse], telaprevir [Incivo], boceprevir [Victrelis], radium Ra223 dichloride [Xofigo]). There were, however, three cancer medicines with sales nearly reaching the sales threshold (pertuzumab [Perjeta], dabrafenib [Tafinlar], and trastuzumab emtansine [Kadcyla]).

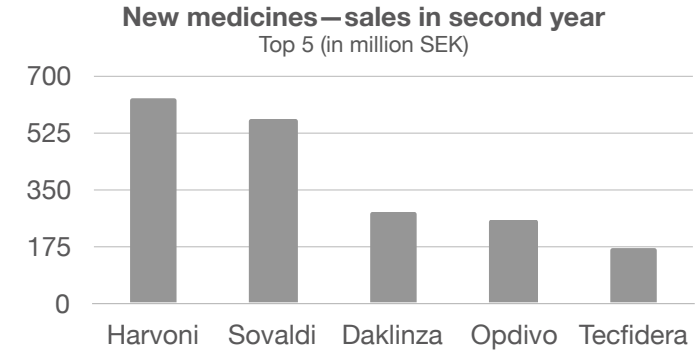
All medicines Processed by EMA: 253		Prioritized medicines Selected by the HS System: 71
83%	Authorized	90%
86%	New active substances	93%
25%	Orphans	20%



L Antineoplastic/immunomodulating agents *A* Alimentary tract/metabolism *J* Antiinfectives for systemic use *N* Nervous system *B* Blood/blood-forming organs



J Antiinfectives for systemic use *L* Antineoplastic/immunomodulating agents *N* Nervous system *S* Sensory organs *C* Cardiovascular system



Harvoni ledispavir/sofosbuvir *Sovaldi* sofosbuvir
Daklinza daclatasvir *Opdivo* nivolumab *Tecfidera* dimethyl fumarate

HS horizon scanning

Figure 8. Description of new medicines comprising the study population

Table 3. Medicines prioritized by the Swedish Horizon Scanning System

Medicinal product	ATC code	Common name	EMA date*	Prioritization date#
Constella	A06AX04	linaclotide	2012-11-26	2012-03-29
Belviq	A08AA11	lorcaserin	[w]2013-05-03	2012-12-13
Mysimba	A08AA62	naltrexone/bupropion	2015-03-26	2015-01-07
Saxenda	A10BJ02	liraglutide	2015-03-23	2014-11-06
Forxiga	A10BK01	dapagliflozin	2012-11-12	2012-02-01
Revestive	A16AX08	teduglutide	2012-08-30	2012-04-13
Brilique	B01AC24	ticagrelor	2010-12-03	2010-06-01
Eliquis	B01AF02	apixaban	2011-05-18	2011-06-07
Brinavess	C01BG11	vernakalant hydrochloride	2010-09-01	2010-11-29
Intuniv	C02AC02	guanfacine	2015-09-17	2015-03-09
Adempas	C02KX05	riociguat	2014-03-27	2014-02-13
Entresto	C09DX04	sacubitril/valsartan	2015-11-19	2015-09-30
Repatha	C10AX13	evolocumab	2015-07-17	2015-05-11
Scenesse	D02BB02	afamelanotide	2014-12-22	2012-02-15
Betmiga§	G04BD12	mirabegron	2012-12-20	2012-08-24
Olysio	J05AE14	simeprevir	2014-05-14	2014-01-30
Incivo	J05AP02	telaprevir	2011-09-19	2011-11-08
Victrelis	J05AP03	boceprevir	2011-07-18	2011-11-08
Sovaldi§	J05AX15	sofosbuvir	2014-01-16	2014-01-24
Jevtana	L01CD04	cabazitaxel	2011-03-17	2010-12-29
Yervoy§	L01XC11	ipilimumab	2011-07-13	2010-08-19
Adcetris	L01XC12	brentuximab vedotin	2012-10-25	2012-06-20
Perjeta	L01XC13	pertuzumab	2013-03-04	2013-01-15
Kadcyla	L01XC14	trastuzumab emtansine	2013-11-15	2013-06-17
Opdivo§	L01XC17	nivolumab	2015-06-19	2015-05-06
Keytruda§	L01XC18	pembrolizumab	2015-07-17	2015-01-21
Cyramza	L01XC21	ramucirumab	2014-12-19	2014-07-02

Medicinal product	ATC code	Common name	EMA date*	Prioritization date#
Zelboraf§	L01XE15	vemurafenib	2012-02-17	2012-02-02
Xalkori	L01XE16	crizotinib	2012-10-23	2012-04-13
Jakavi	L01XE18	ruxolitinib	2012-08-23	2012-06-25
Stivarga	L01XE21	regorafenib	2013-08-26	2013-03-18
Masiviera	L01XE22	masitinib	R2014-05-22	2013-07-03
Tafinlar	L01XE23	dabrafenib	2013-08-26	2013-06-11
Mekinist	L01XE25	trametinib	2014-06-30	2013-12-11
Imbruvica§	L01XE27	ibrutinib	2014-10-21	2014-08-28
Vargatef	L01XE31	nintedanib	2014-11-21	2014-09-10
Ofev	L01XE31	nintedanib	2015-01-15	2015-04-07
Tekinex	L01XX40	omacetaxine mepesuccinate	W2011-01-11	2011-04-27
Erivedge	L01XX43	vismodegib	2013-07-12	2013-01-03
Zaltrap	L01XX44	aflibercept	2013-02-01	2012-09-25
Kyprolis§	L01XX45	carfilzomib	2015-11-19	2015-10-07
Lynparza	L01XX46	olaparib	2014-12-16	2014-05-07
Imlygic	L01XX51	talimogene laherparepvec	2015-12-16	2015-05-11
Xtandi§	L02BB04	enzalutamide	2013-06-21	2013-01-29
Zytiga§	L02BX03	abiraterone	2011-09-05	2011-10-18
Lympreva	L03AX	dasiprotimut-t	R2015-07-03	2015-03-12
Benlysta	L04AA26	belimumab	2011-07-13	2011-06-01
Gilenya§	L04AA27	fingolimod	2011-03-17	2010-12-22
Nulojix	L04AA28	belatacept	2011-06-17	2011-05-24
Aubagio	L04AA31	teriflunomide	2013-08-26	2012-10-22
Otezla§	L04AA32	apremilast	2015-01-15	2014-12-09
Entyvio§	L04AA33	vedolizumab	2014-05-22	2014-02-20
Lemtrada	L04AA34	alemtuzumab	2013-09-12	2013-04-10
Movectro	L04AA40	cladribine	W2011-02-08	2010-12-22
Cosentyx§	L04AC10	secukinumab	2015-01-15	2014-12-09

Medicinal product	ATC code	Common name	EMA date*	Prioritization date#
Prolia	M05BX04	denosumab	2010-05-26	2010-04-29
Xiapex	M09AB02	collagenase Clostridium histolyticum	2011-02-28	2010-12-06
Translarna	M09AX03	ataluren	2014-07-31	2013-12-18
Fampyra	N07XX07	fampridine	2011-07-20	2011-05-24
Vyndaqel	N07XX08	tafamidis	2011-11-16	2011-10-31
Tecfidera§	N07XX09	dimethyl fumarate	2014-01-30	2013-02-15
Nerventra	N07XX10	laquinimod	R2014-08-19	2013-07-03
Anoro	R03AL03	umeclidinium bromide/vilanterol	2014-05-08	2014-02-09
Daxas	R03DX07	roflumilast	2010-07-05	2010-09-15
Nucala	R03DX09	mepolizumab	2015-12-02	2015-04-22
Kalydeco	R07AX02	ivacaftor	2012-07-23	2012-07-26
Orkambi	R07AX30	lumacaftor/ivacaftor	2015-11-19	2015-06-09
Eylea§	S01LA05	aflibercept	2012-11-22	2012-05-18
Praxbind	V03AB37	idarucizumab	2015-11-20	2015-10-13
Xofigo	V10XX03	radium Ra223 dichloride	2013-11-13	2013-03-26
Qsiva	—	phentermine/topiramate	R2013-05-14	2011-10-18

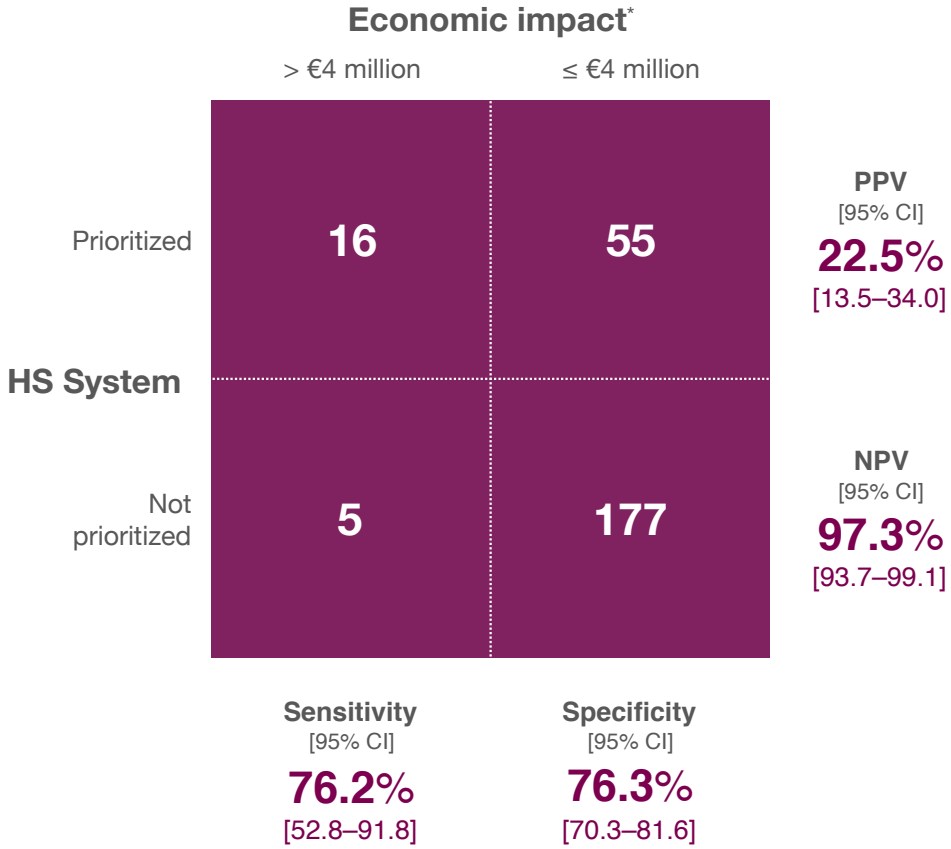
ATC anatomical therapeutic chemical classification system
* EMA marketing authorization date, or EMA refusal date, or date of withdrawal of the initial marketing authorization application
# Prioritization made by the Swedish Horizon Scanning System; date of early assessment report publication
§ Medicinal product with sales > €4 million in the second year on the market
W Withdrawal of marketing authorization application
R Refusal of marketing authorization application

Table 4. Medicines not prioritized by the Swedish Horizon Scanning System

Medicinal product[§]	ATC code	Common name	EMA date[*]
Elocta	B02BD02	efmoroctocog alfa	2015-11-19
Opsumit	C02KX04	macitentan	2013-12-20
Triumeq	J05AR13	abacavir sulfate/dolutegravir sodium/lamivudine	2014-09-01
Daklinza	J05AX14	daclatasvir	2014-08-22
Harvoni	J05AX65	ledipasvir/sofosbuvir	2014-11-17

ATC anatomical therapeutic chemical classification system
[§] Medicinal products with sales > €4 million in the second year on the market
[*] EMA marketing authorization date

A breakdown of the study population by prioritization status and economic impact as well as the calculated sensitivity, specificity, positive predictive value, and negative predictive value are provided in Figure 9.



CI confidence interval *HS* horizon scanning *NPV* negative predictive value
PPV positive predictive value
[*] In the second year on the market

Figure 9. Tabulation by prioritization status and economic impact

4.2 STUDY II

In Study I it was observed that the Swedish Horizon Scanning System prioritized nine new medicines intended for use in patients with multiple sclerosis. Two of these—fampridine (Fampyra) and cannabinoids (Sativex)—were treatments limited to the management of symptoms. The other seven medicines were disease-modifying treatments: fingolimod (Gilenya), cladribine (Movectro), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), alemtuzumab (Lemtrada), laquinimod (Nerventra), and daclizumab (Zinbryta). While the original marketing authorization application for cladribine was withdrawn, in 2017 the medicine was eventually granted marketing authorization by EMA under the brand name Mavenclad. The marketing authorization application for laquinimod, however, was refused by EMA due to an unfavorable benefit–risk assessment.

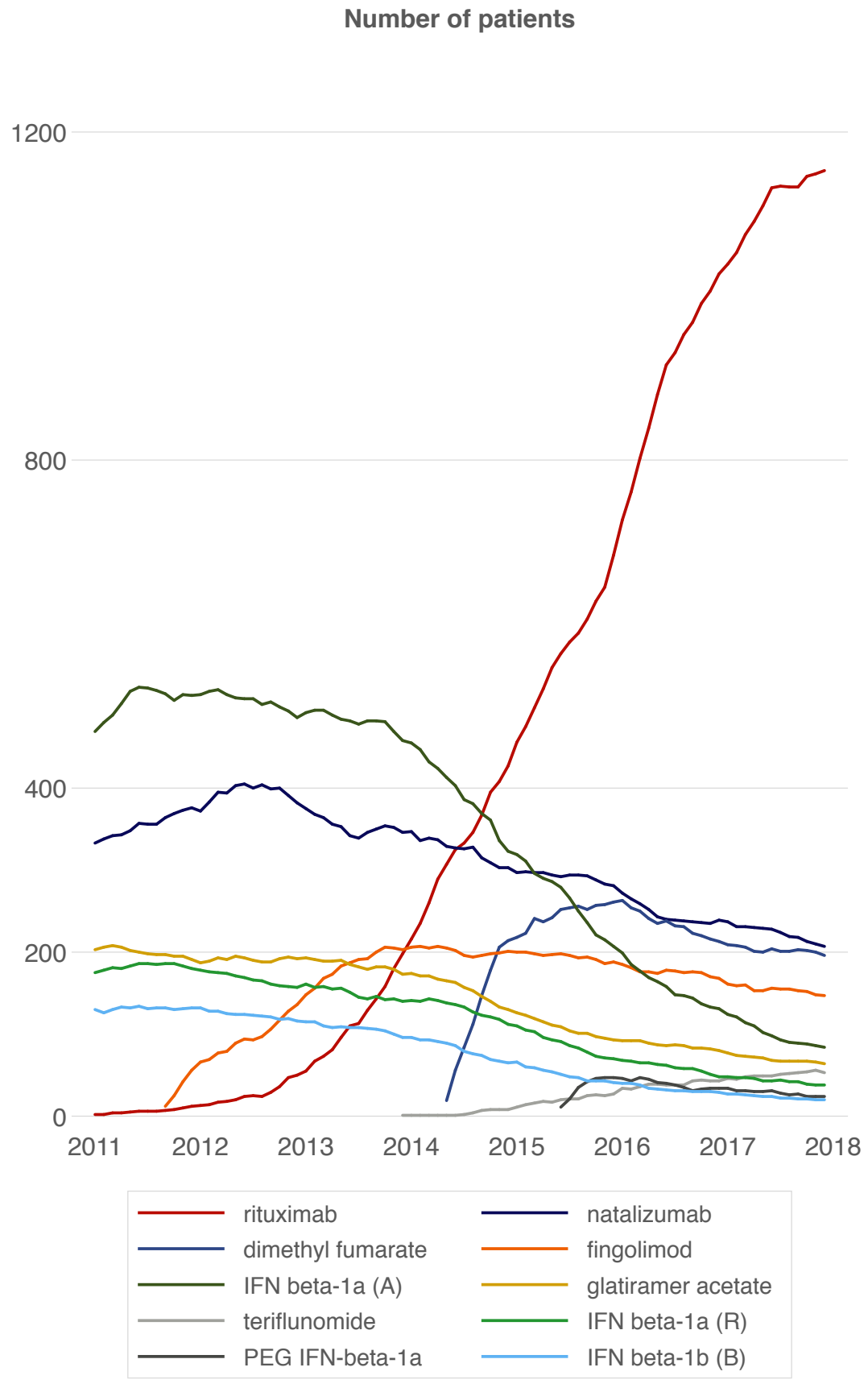
Two additional disease-modifying treatments used in multiple sclerosis were not prioritized by the Swedish Horizon Scanning System. During the study period off-label use of rituximab in multiple sclerosis patients increased steadily. Also, in 2014, peginterferon beta-1a (Plegridy) was granted marketing authorization by EMA.

Utilization trends of multiple sclerosis disease-modifying treatments are presented in Figure 10. There was a limited uptake of alemtuzumab, teriflunomide, peginterferon beta-1a, and daclizumab—neither accounted for more than 5% of disease-modifying treatment use in multiple sclerosis patients in any given month. Therefore, these products were not included as interventions in the interrupted time series analyses.

The analyses showed that reimbursement of fingolimod and reimbursement of dimethyl fumarate were both associated with changes in utilization patterns of other disease-modifying treatments.

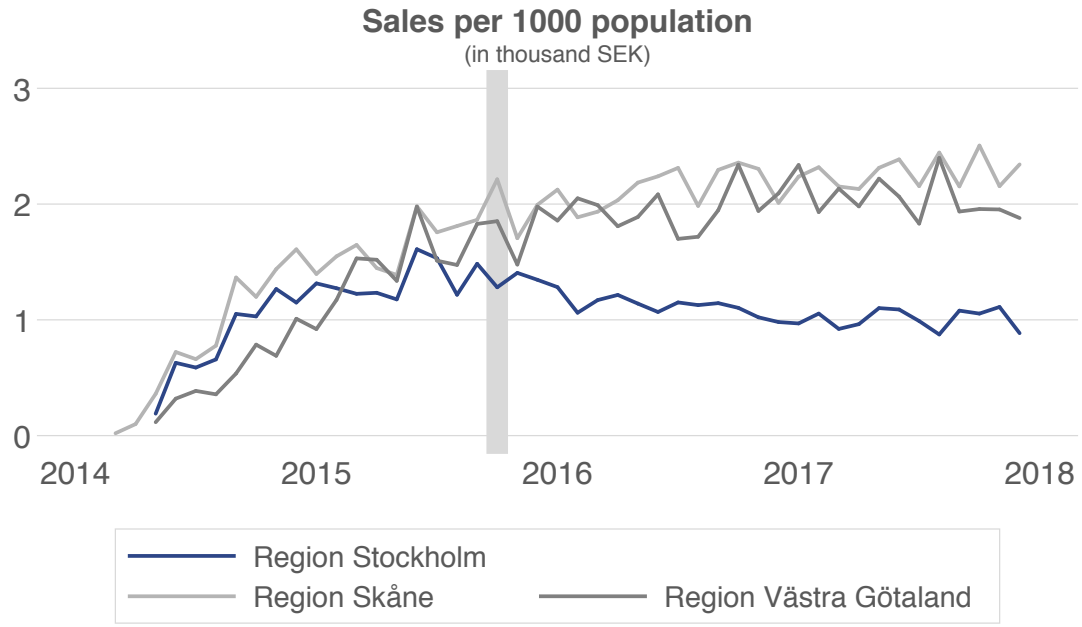
The local recommendation on rituximab was associated with increasing use of rituximab. The regional drug and therapeutics committee recommendation on dimethyl fumarate had no direct effect on its use. However, shortly after the recommendation a clear downward trend in dimethyl fumarate use was observed.

Additional analyses based on monthly sales data were also conducted to describe dimethyl fumarate utilization trends in the three largest regions in Sweden. Sales per 1000 population were calculated to account for differences in population size (Figure 11). While rapid uptake was observed in all three regions, the utilization trends diverged following the month of the treatment recommendation issued in Region Stockholm.



A Avonex *B* Betaferon *IFN* interferon *R* Rebif
Monthly data

Figure 10. Number of prevalent multiple sclerosis disease-modifying treatment users



DTC drug and therapeutics committee
Monthly data

The month of the regional DTC recommendation on how dimethyl fumarate should be used in Region Stockholm is indicated by the vertical bar

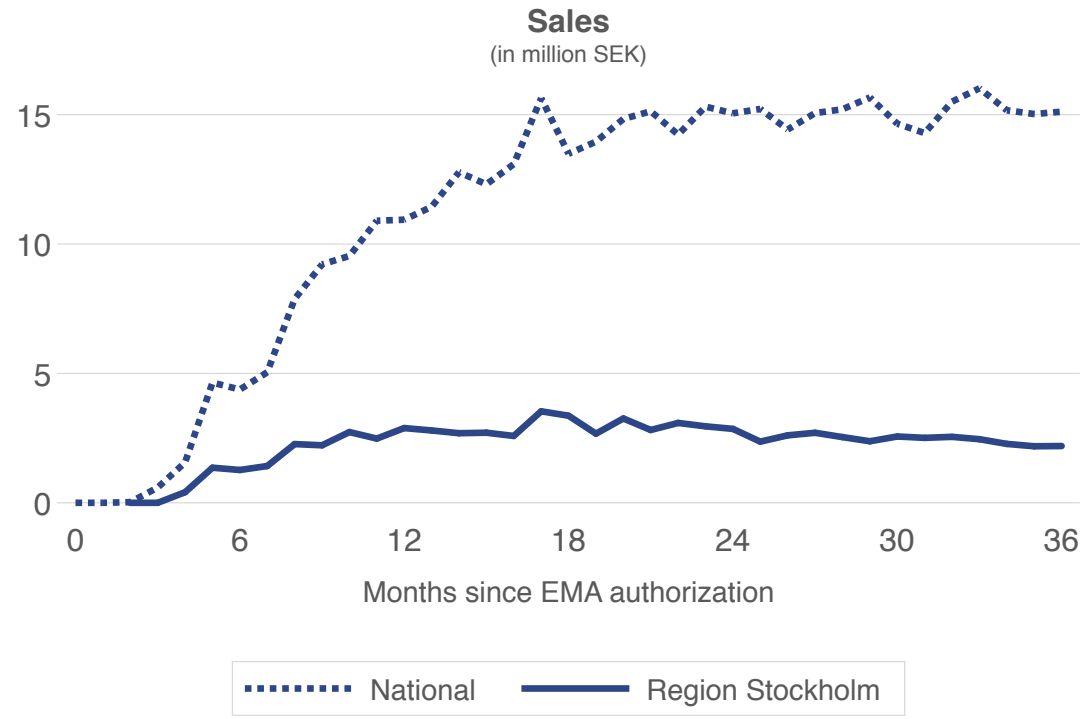
Figure 11. Sales of dimethyl fumarate in the three largest regions

4.3 STUDY III

Dimethyl fumarate—the first oral disease-modifying treatment approved as a first-line treatment option for relapsing-remitting multiple sclerosis patients—was the subject of Study III. The study provided the opportunity to look into the use of real-world data in a disease area with a number of medicines administered exclusively in the hospital setting.

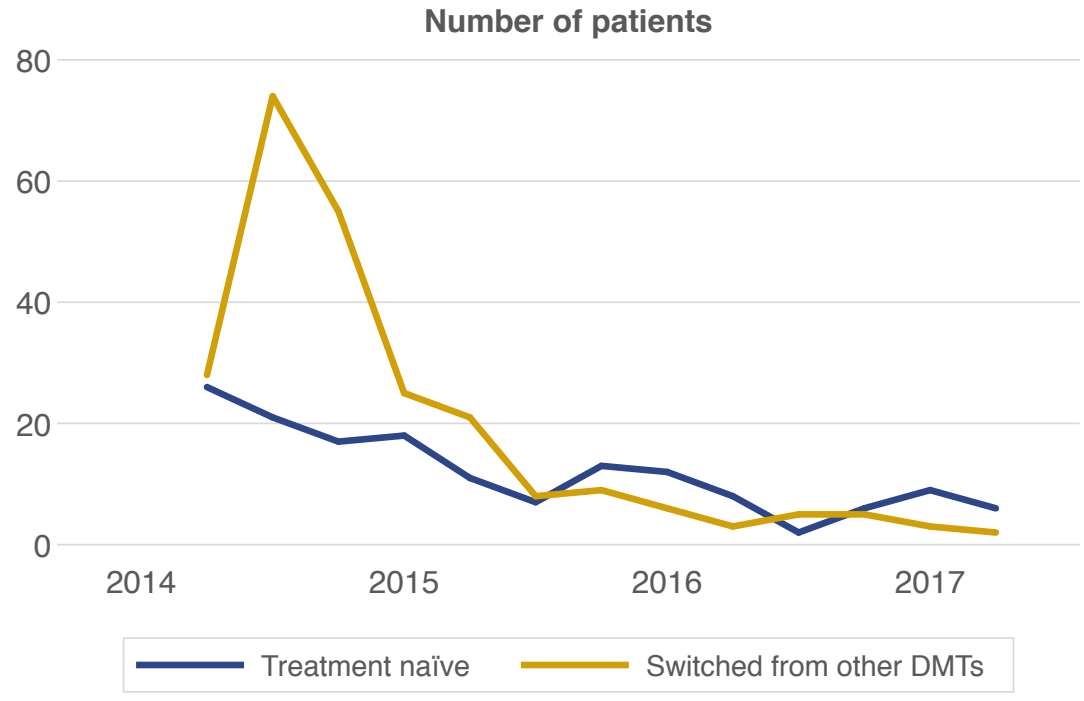
On 15 February 2013 dimethyl fumarate was prioritized by the Swedish Horizon Scanning System. The marketing authorization application was approved by EMA on 30 January 2014. Only three months later dimethyl fumarate was included by the TLV in the pharmaceutical benefits scheme and made available for broad use in relapsing-remitting multiple sclerosis patients. Region Stockholm included dimethyl fumarate in the managed introduction process. There was no recorded use of dimethyl fumarate in the region prior to the TLV decision date (9 May 2014).

Dimethyl fumarate had a rapid market uptake both at the regional and national level in Sweden. Nationally, during the first three years on the market, total sales amounted to SEK 413 million (Figure 12). As per the definition used in Study I, the medicine was classified as having substantial economic impact on the healthcare system. In its second year on the Swedish market it was the highest grossing medicinal product behind only the new hepatitis C medicines.



Monthly data

Figure 12. Sales of dimethyl fumarate

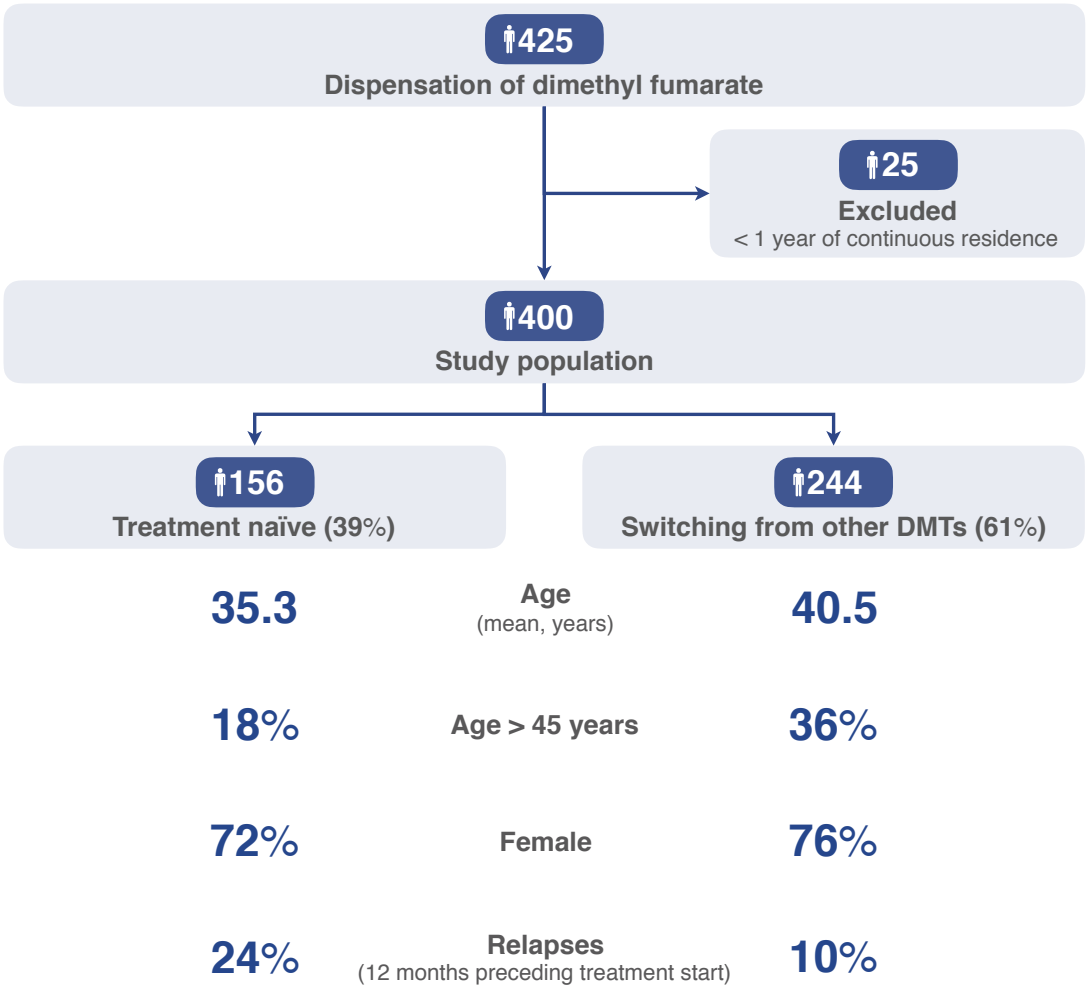


DMT disease-modifying treatment
Quarterly data

Figure 13. Dimethyl fumarate initiation patterns

A majority of patients had been treated with other disease-modifying treatments prior to initiating treatment with dimethyl fumarate. Initiation patterns of dimethyl fumarate are illustrated in Figure 13.

During the study period 425 patients initiated treatment with dimethyl fumarate in Region Stockholm. Study selection criteria were met by 400 patients (Figure 14). Baseline characteristics are presented below and in Figure 15.



DMT disease-modifying treatment

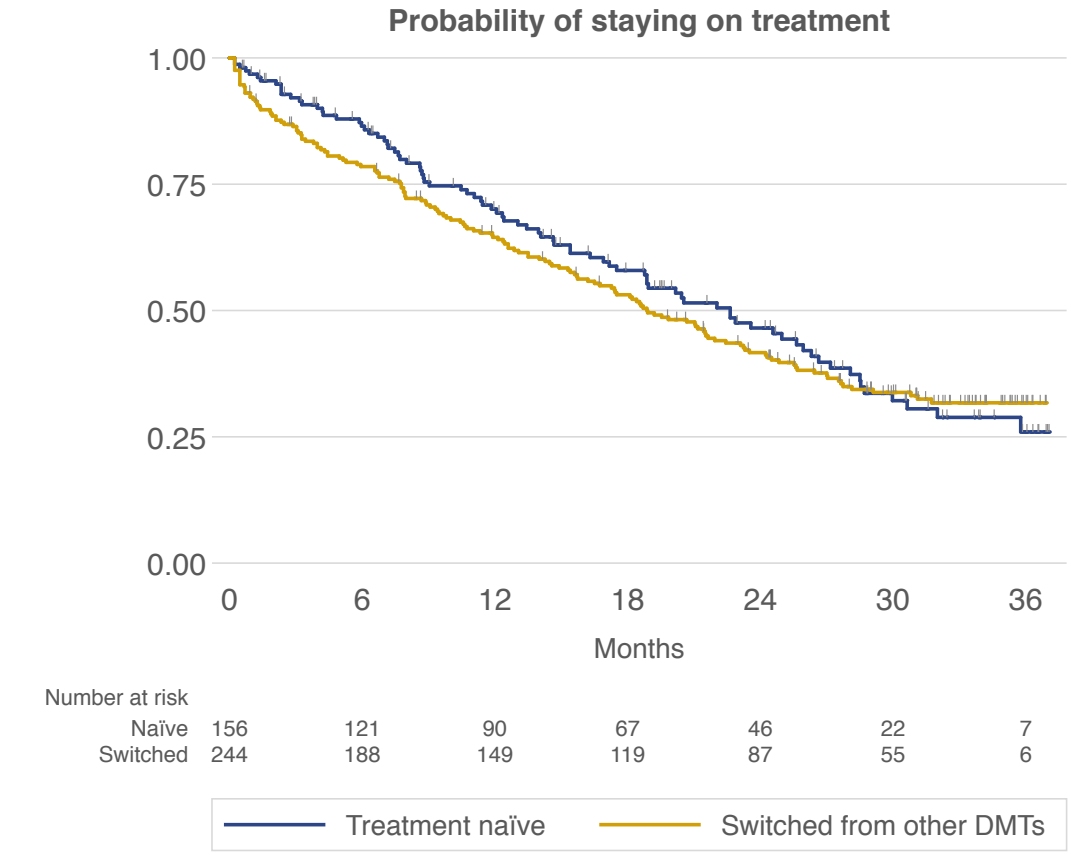
Figure 14. Characteristics of patients initiating dimethyl fumarate

Treatment naïve Number of patients: 156		Switching from other DMTs Number of patients: 244
	Use of medicines at time of dimethyl fumarate initiation	
12%	**Opioids**	11%
13%	**Other pain medicines**	50%
8%	**Antiepileptics**	7%
12%	**Anxiolytics**	12%
22%	**Hypnotics and sedatives**	20%
12%	**Antidepressants**	22%
3.4	**Classes of medicines** (mean, dispensed past 12 months)	6.0
	Healthcare encounters during the 12 months preceding treatment start	
49%	**≥ 1 hospital admission**	21%
0.7	**Hospital admissions** (mean)	0.4
5.8	**Outpatient specialist visits** (mean)	5.4
2.3	**Primary care visits** (mean)	2.2

DMT disease-modifying treatment

Figure 15. Use of medicines and healthcare resource utilization in patients treated with dimethyl fumarate

Treatment persistence estimates are plotted in Figure 16. The probability of staying on treatment with dimethyl fumarate at two years was 46% among treatment-naïve patients and 40% among those who had previously been treated with another disease-modifying treatment.



DMT disease-modifying treatment
Hash marks indicate censoring

Figure 16. Persistence with dimethyl fumarate

4.4 STUDY IV

Targeted cancer medicine olaparib—the first approved poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor—was the subject of Study IV. In this study national-level data were used to assess the real-world use and outcomes of olaparib.

Olaparib was prioritized on 7 May 2014 by the Swedish Horizon Scanning System, and approved on 14 December 2014 by EMA for use in ovarian cancer. Less than three months later, on 25 February 2015, it was included by the TLV in the pharmaceutical benefits scheme. This product was also included in the national process for the managed introduction of new medicines. The time between the marketing authorization approval by EMA and the first use by patients in Sweden was only two months. There was no record of use of olaparib prior to its inclusion in the pharmaceutical benefits scheme.

During the first three years on the market in Sweden, over 100 patients were treated with olaparib with sales amounting to SEK 46 million (Figure 17). While olaparib was not classified as having substantial economic impact based on the definition used in Study I, the Swedish Horizon Scanning System had prioritized the medicine as it was judged to be an innovative approach to treatment of ovarian cancer.

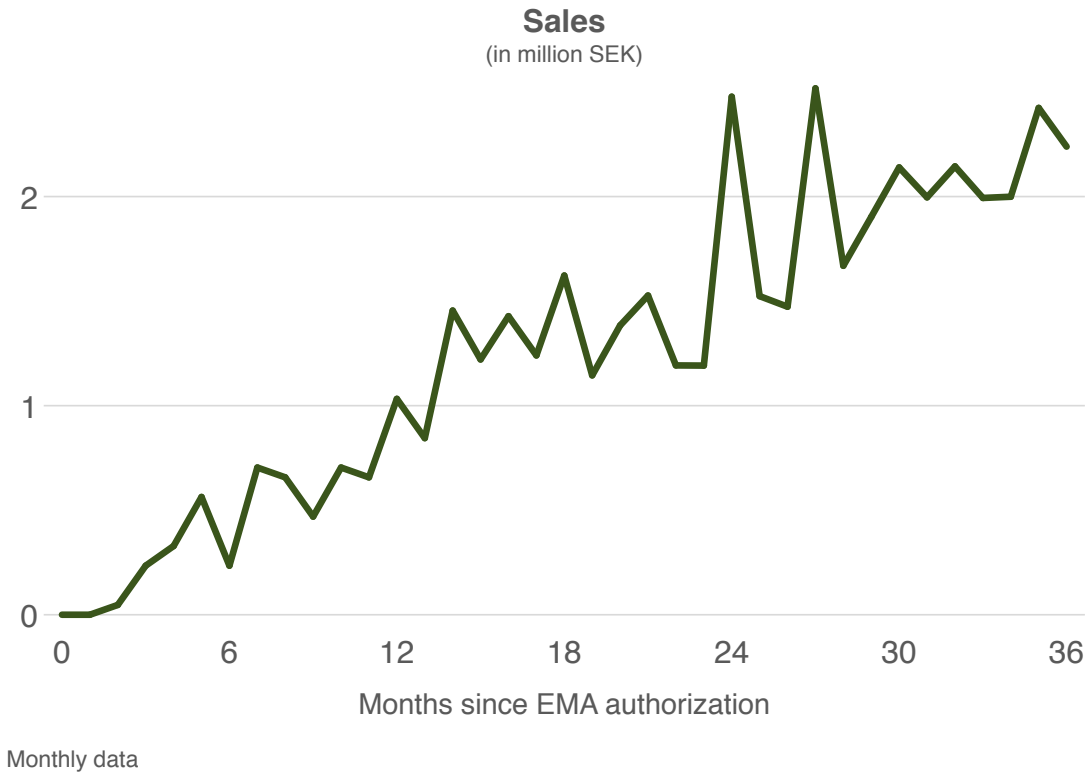


Figure 17. National sales of olaparib

Characteristics of patients who were dispensed olaparib are presented in Figure 18.

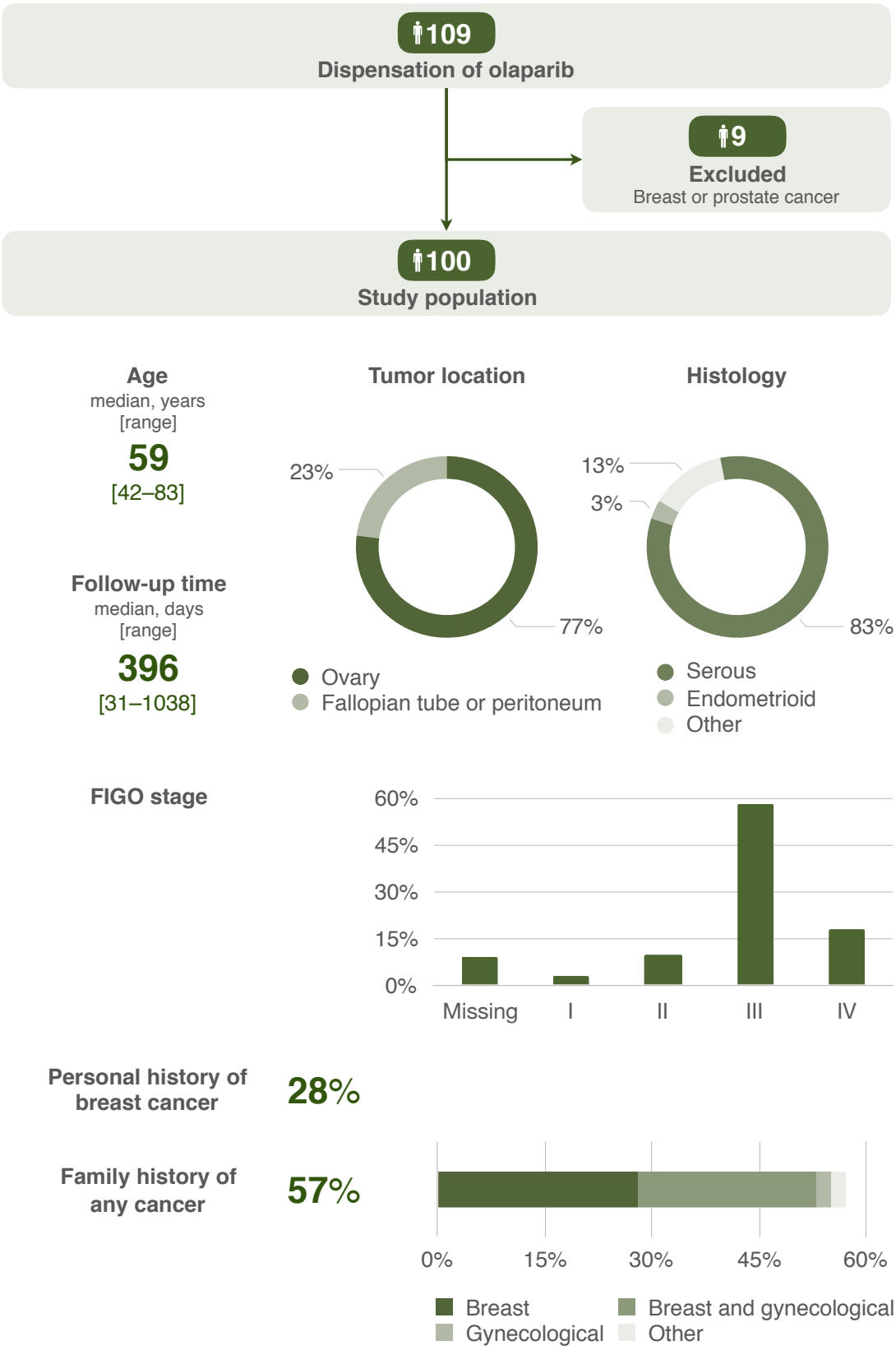


Figure 18. Characteristics of ovarian cancer patients initiating olaparib

Fifty-seven patients discontinued olaparib during the follow-up period. Median time to olaparib discontinuation was 9.5 months (Figure 19) and median overall survival was 33.0 months (Figure 20).

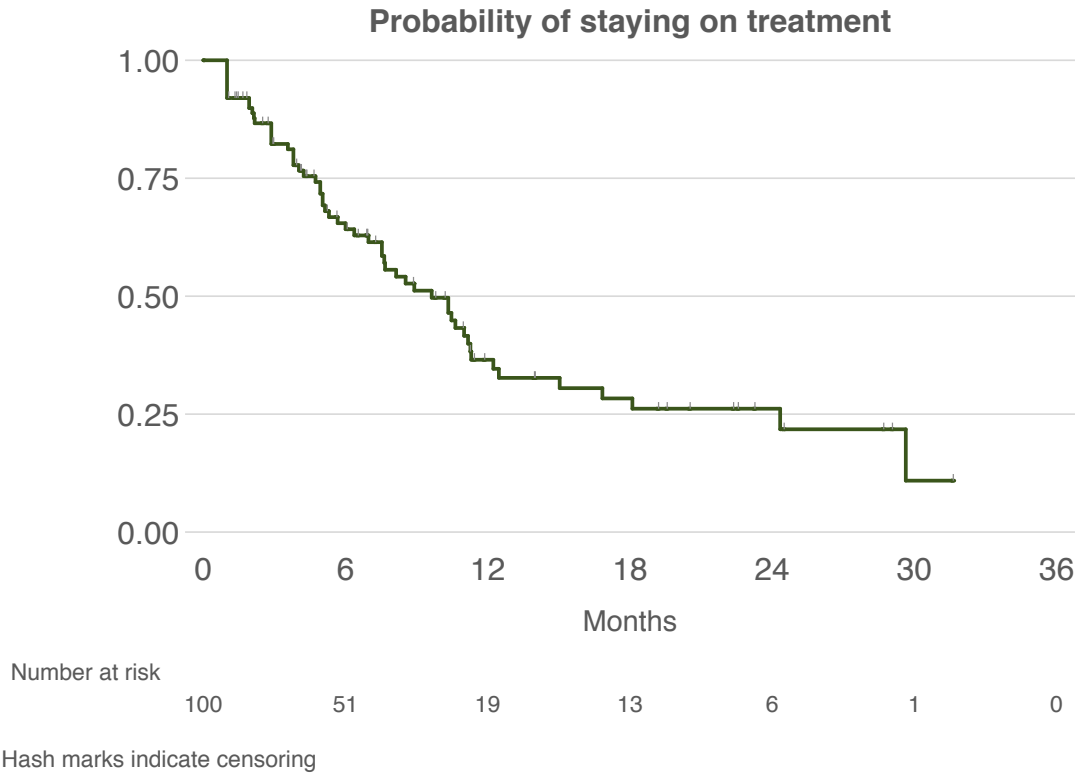


Figure 19. Time to treatment discontinuation in ovarian cancer patients treated with olaparib

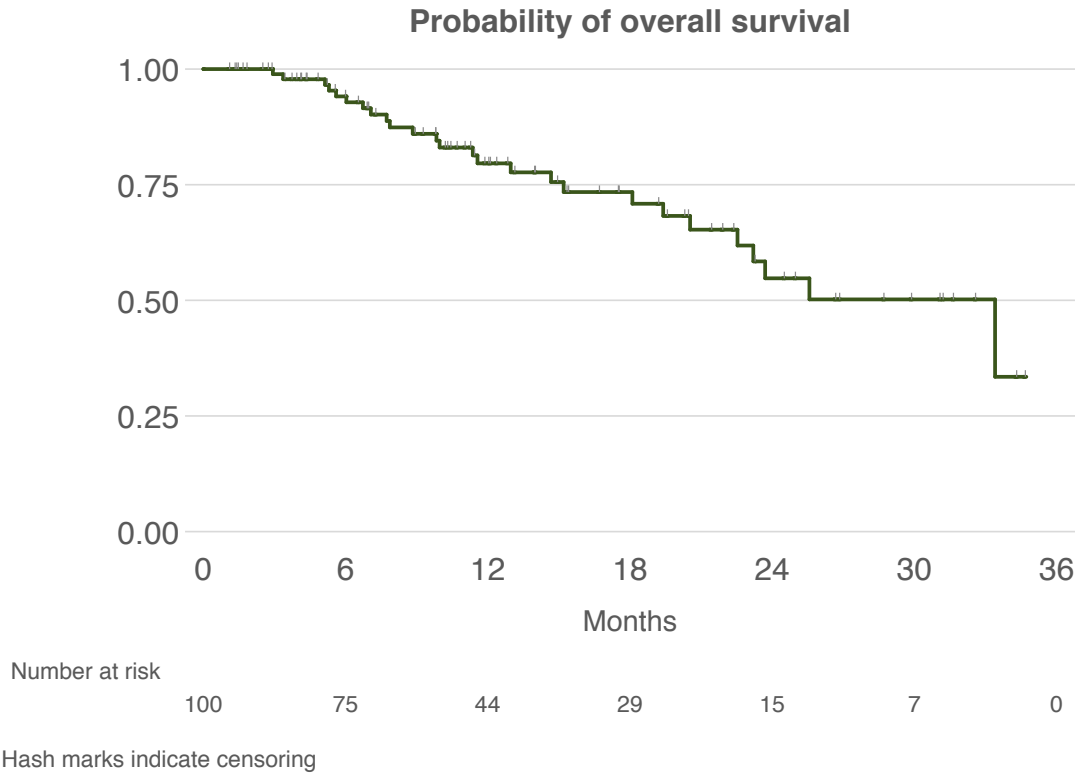


Figure 20. Overall survival in ovarian cancer patients treated with olaparib

5 DISCUSSION

In the pursuit of the important aim of improving patient outcomes and experience of care while managing constrained budgets, payers and providers seek to enable appropriate and sustainable access to new medicines. Various policy options exist to help facilitate this. For example, a recent report by the Organisation for Economic Cooperation and Development (OECD) listed horizon scanning, use of measures to encourage rational prescribing, as well as assessment of medicines in routine clinical practice among possible policy options that healthcare systems may adopt to facilitate rational use of new medicines [45]. Such initiatives, however, should be informed by research and be subject to continuous evaluation [118].

This thesis examined selected elements of the process for managed introduction of new medicines that have been used in Sweden for at least a decade. This chapter discusses the evaluation of the horizon scanning system, the impact of treatment recommendations, and the utility of regional and national data sources for the assessment of new specialist medicines in routine clinical practice.

5.1 EVALUATION OF HORIZON SCANNING

Horizon scanning activities have been carried out in Sweden since the mid-2000s. Since then the horizon scanning process has evolved and adapted to meet the needs of its customers with considerable knowledge and skills acquired along the way.

It was warranted, therefore, to share a detailed description of the Swedish Horizon Scanning System with wider audiences, both in Sweden and internationally. Upon reviewing publicly accessible information on horizon scanning work conducted in other countries [119–125] and completing the review on the evolution of horizon scanning in Sweden it became clear that there are many similarities across systems [53]. This is not surprising for at least two reasons. First, at its inception the Swedish Horizon Scanning System was advised and supported by the United Kingdom's National Institute for Health Research (NIHR) Horizon Scanning Research and Intelligence Centre (HSC) [53]. The NIHR HSC was also among the founder members of the EuroScan International Network and played a pivotal role in defining and developing horizon scanning methods [119, 126–130]. Second, once established, the Swedish Horizon Scanning Working Group, in its turn, shared experiences with stakeholders from other countries, including Denmark, Belgium, the Netherlands, Luxembourg, and Austria [131].

Given that the Swedish Horizon Scanning System may be viewed as an exemplar internationally [41] and that it has a clear influencing role in the national process for managed introduction of new medicines [53], an evaluation of its performance was necessary. The selection of a study design for the evaluation was informed by a comprehensive literature review.

While many horizon scanning systems have been described in the literature, only four evaluations were identified. These were the evaluations of the NIHR HSC [105, 132], the Austrian Horizon Scanning Programme [133], and the United States Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System [134]. The Austrian Horizon Scanning Programme was assessed in a qualitative study comprising a survey, a download analysis, an environmental analysis, and an online questionnaire to evaluate user satisfaction [133]. Quantitative methods have also been used in the evaluation of horizon scanning activities. The accuracy of prioritization made by the NIHR HSC was assessed twice based on an approach used in diagnostic test accuracy studies [105, 132]. Finally, the AHRQ Healthcare Horizon Scanning System was evaluated using both qualitative and quantitative methods that were similar to those used in the evaluations of the Austrian and the NIHR HSC systems [134]. In addition, the EuroScan Methods Toolkit [135] and a published evaluation framework [126] provided valuable insights for the development of the study design for the Swedish evaluation. Upon reviewing available options, it was decided to focus on assessing the accuracy of the system.

A number of specific features of the Swedish Horizon Scanning System had to be accounted for in the design of the study. Among them, the broad range of prioritization criteria used in the filtration and prioritization steps posed a challenge. The decision to prioritize a new medicine is binary—a medicine is either prioritized or not. The assessment of the accuracy of prioritization therefore required a binary reference classification of all new medicines. As a reference standard, national sales data were used to classify new medicines according to their economic impact. Narrowing down the assessment to the accuracy of the prioritization of new medicines with substantial economic impact not only provided a feasible approach to quantitatively assess the entire output of the Swedish Horizon Scanning System but also addressed the important question of whether payers were informed of such impactful medicines ahead of their launch. The pros and cons of using sales data as a reference standard have been discussed in the publication [136]. It should also be noted that this evaluation approach allowed for a quantitative and reproducible assessment of both inpatient and outpatient medicines across all therapeutic areas.

The assessment of the accuracy of the Swedish Horizon Scanning System showed that all new medicines processed by EMA were identified. Of these 253 new medicines, 71 were prioritized and 21 were classified as having substantial economic impact based on the reference standard. Of these 21 medicines, five were not prioritized. However, as discussed in the publication, these medicines were identified by the system but not selected for early assessment because similar medicines had already been prioritized or marketed [136]. Among the medicinal products classified as having substantial economic impact, almost all were specialist medicines. New cancer medicines comprised over one third of these. Overall, many new cancer medicines also had an orphan designation. Moreover, the analyses of sales data showed that, outside of the

new medicines for hepatitis C, dimethyl fumarate, the utilization of which was explored in depth in Study III, was the highest grossing new medicine in Sweden.

In addition to the assessment of accuracy, other aspects of the Swedish Horizon Scanning System may also warrant evaluation. The EuroScan Methods Toolkit suggests that evaluations should be thought of as a progressive activity taking place in several dimensions [135]. Aspects that could be explored include user satisfaction and the use of the outputs for decision making. Moreover, gaining insights on how the filtration and prioritization criteria are applied may help to identify alternative approaches to defining a reference standard for use in future accuracy assessments. In addition, a comprehensive review of the content and impact of early assessment reports may further contribute to a better understanding of the overall effectiveness of the system.

It is expected that horizon scanning in Sweden will continue to evolve as a response to both health innovation and policy initiatives. For example, the scope of the Swedish Horizon Scanning System could be expanded to identify other health technologies such as medical devices and diagnostics [137–139]. Furthermore, identification of disinvestment opportunities could also help payers and providers to optimize the provision of healthcare services [140]. Moreover, as healthcare systems move toward patient and person-centeredness it may be warranted to facilitate patient and public involvement in horizon scanning activities [141]. Finally, providing support to cross-national collaborations, including the ongoing health technology assessment initiatives EUnetHTA [142], FINOSE [143], and BeNeLuxA [144], may also bring benefits [145].

5.2 IMPACT OF TREATMENT RECOMMENDATIONS

The treatment recommendations issued by the regional drug and therapeutics committees have become a well-established tool for facilitating rational use of both new and established medicines [146]. Specialists in hospitals may also issue local recommendations focusing on steering the use of medicines within their clinics. Moreover, within the national process for managed introduction of new medicines, the New Therapies Council can develop national treatment recommendations, typically on specialist medicines, to facilitate rational and equitable use across the regions.

The regional drug and therapeutics committees initially focused on facilitating rational use of established medicines, particularly those prescribed in primary care [63, 68, 147]. It has, however, been recognized that evidence-based treatment recommendations can also enable rational introduction of new medicines [66]. For example, as part of the model for managed introduction of new medicines in Region Stockholm, treatment recommendations have been used to steer the prescribing of weight loss medicines [148–150] and oral anticoagulants [67], both largely prescribed by general practitioners [150, 151]. It has however been shown that different factors may drive the adoption of new medicines across healthcare settings [152] and that

general practitioners and specialists may vary in their response to treatment recommendations [153, 154]. Given that a considerable share of new medicines is intended for use in the specialized care setting, research into the impact of treatment recommendations on specialist prescribing was warranted.

As was seen in Study I, several new medicines were introduced for the treatment of relapsing-remitting multiple sclerosis. To help steer the use of these medicines, treatment recommendations were issued at the local and regional level. The availability of continuously recorded individual-level data on inpatient and outpatient use of disease-modifying treatments in all multiple sclerosis patients residing in the region provided an opportunity to assess the impact of these recommendations using an interrupted time series design. An alternative analytical approach to the one used could have been a comparative interrupted time series design [155] that would have included a control series from another region in which no specific activities were undertaken to steer the prescribing of rituximab and dimethyl fumarate. However, it was not possible to obtain a complete overview of the utilization of disease-modifying treatments in other regions because data on inpatient use of medicines were not readily available in databases at the national level. Nonetheless, national monthly sales data on dimethyl fumarate were used to describe trends in the three largest regions in Sweden. These descriptive analyses demonstrated that dimethyl fumarate use in Region Stockholm was the lowest with noticeable differences emerging following the treatment recommendation. The impact of the recommendations as well as strengths and limitations of the analyses are discussed further in the publication [156].

Among the recently introduced multiple sclerosis medicines, only fingolimod and dimethyl fumarate impacted the utilization of disease-modifying treatments. Notably, in Study I, fingolimod and dimethyl fumarate were classified as requiring prioritization. The alignment of these findings lends support to the utility of using sales data as a reference standard for assessing horizon scanning accuracy. Rituximab, repurposed for the treatment of multiple sclerosis, was however not prioritized by the Swedish Horizon Scanning System even though scanning for new indications of existing medicines is within its scope. This can be explained, however, by the fact that no marketing authorization application for the use of rituximab in this indication had been submitted.

In addition to the assessment of treatment recommendations in multiple sclerosis conducted as part of this thesis, two other recent studies also explored the impact of treatment recommendations on the use of new medicines in Sweden. Treatment recommendations issued as part of the regional managed introduction of non-vitamin K antagonist oral anticoagulants were found to be influential in the choice of anticoagulants prescribed [67]. At the national level, it was shown that prescribers adhered to the recommendations on the use of new direct-acting antivirals for treatment of hepatitis C [70]. In summary, these findings indicate that evidence-based treatment recommendations can support the rational introduction and use of new medicines, including those used in the specialized care setting.

5.3 ASSESSMENT OF THE USE AND OUTCOMES OF NEW MEDICINES USING HEALTHCARE DATABASES

Routine clinical care in Sweden generates real-world data that for decades have been used to inform decision making [157–166]. The establishment of the Prescribed Drug Register enabled nation-wide observational research on the use and outcomes of prescribed medicines [101, 167, 168]. In addition, some of the new medicines used in hospitals have been recorded in patient registries [169, 170]. Historically, most observational research was conducted by academics and clinicians. Payers and providers have also been increasingly making use of available data to support decision making [37, 66, 171, 172]. The interest in leveraging real-world data continues to grow and new uses are being explored by various stakeholders.

Assessment of the use and outcomes of new medicines is an important part of the process for managed introduction [51, 53]. Among the new medicines prioritized by the Swedish Horizon Scanning System, dimethyl fumarate and olaparib were included as pilots in the managed introduction process. Studies III and IV explored the utility of existing healthcare databases for addressing questions about the real-world use and outcomes of specialist medicines using dimethyl fumarate and olaparib as examples.

Studies III and IV therefore fulfilled two purposes. First, these studies described the use and assessed the outcomes of treatment with dimethyl fumarate and olaparib. Second, the studies highlighted both opportunities and challenges of using healthcare databases for conducting studies on new medicines used in the specialized care setting. A thorough discussion of the uptake, utilization, and outcomes of treatment with dimethyl fumarate in relapsing-remitting multiple sclerosis patients and with olaparib in ovarian cancer patients is provided in the publications [173, 174]. Moreover, the publications include a discussion on differences between the observations from routine care and the results of the pivotal clinical trials and also cover study-specific strengths and limitations.

Given the scope of this thesis, the remainder of this section focuses on the utility of existing healthcare databases for supporting the process for managed introduction of new medicines in Sweden.

At the outset of a research project initiated to support decision making it is of critical importance to define the research question. A well-defined research question is necessary to guide subsequent decisions around study design and data needs. At the time of the introduction of a new medicine, there is a need to assess whether it is used appropriately, with the definition of "appropriate" being context-dependent, and also to gain an understanding of the medicine's value in routine clinical practice. Some questions can be answered with existing healthcare databases, while others may require primary data collection.

Dimethyl fumarate was the first oral disease-modifying treatment approved for use as a first-line option in relapsing-remitting multiple sclerosis patients. Other first-line treatment alternatives available at the time of its introduction were injectable

treatments (interferon betas and glatiramer acetate). While more expensive than the other treatments, dimethyl fumarate was perceived to be more effective. However, there were also concerns about the relatively high dropout rates reported in the clinical trials. Therefore, it was considered necessary to monitor the uptake and to assess persistence with dimethyl fumarate in routine clinical practice.

The decision to use the existing healthcare databases of Region Stockholm was supported by earlier research that had validated the use of procedure codes to identify multiple sclerosis disease-modifying treatments administered in hospitals [175]. By combining the hospital data with data on medicines dispensed in pharmacies it was possible to provide a complete description of the utilization of all disease-modifying treatments at the individual level. This allowed to assert the line of treatment in which dimethyl fumarate was used. Moreover, it provided more accurate estimates of treatment persistence, given that switching to medicines administered in hospitals was common. This type of population-based research opportunity is however rare [176].

Olaparib was the first PARP inhibitor to be approved for treatment of ovarian cancer. The Swedish Horizon Scanning System prioritized olaparib as an innovative treatment [136]. Among many new cancer medicines, olaparib was subsequently included as the first cancer medicine to go through the national process for managed introduction and follow-up. Given the national scope of this project, the existing national population-based registers were chosen as the data source. Disease registries may also contain useful data; such data sources should be explored in future studies.

The Prescribed Drug Register provided data on all dispensed packages of olaparib, free-text documentation on directions for use, and the use of concomitant medicines to manage side effects. Because data on medicines administered in hospitals are generally not available in the population-based registers, monthly sales data were reviewed to estimate the use of olaparib in the hospital setting. The national Cancer Register, which includes records on all new cancer cases, provided information on the tumor site, histological type, and stage. Importantly, these data allowed for the identification of off-label use of olaparib. Finally, access to up-to-date death records enabled robust estimation of overall survival [103], something that internationally is generally not possible [177].

Several common challenges were encountered in the assessment of both dimethyl fumarate and olaparib. These include a lack of data on the use of medicines in hospitals, limited recording of clinical data, and reliance on the accuracy and completeness of the available information.

While opportunities exist for the documentation of medicines administered in hospitals, these medicines are currently not captured consistently at the individual level. Hence, in light of the evidentiary needs to monitor the utilization, effectiveness, safety, and value of new medicines, many of which increasingly are administered in the hospital setting, there is a need to facilitate systematic recording of these medicines across hospitals and therapeutic areas.

Limited access to clinical data makes it difficult to assess whether the use of medicines can be judged as appropriate and to study relevant outcomes. Examples of relevant data that were either not readily available or of inconsistent quality include reasons for treatment discontinuation, findings from medical imaging and genetic testing, and evaluations of disease status and progression. Data from electronic health records, that have been implemented nationally since 2012, have the potential to fill some of these data gaps. However, the use of electronic health records for research requires functions to ensure accuracy and completeness of the collected data [75]. Furthermore, the use of different electronic health record systems and fragmented access can impact usability of the data.

It should always be kept in mind that any observational study based on secondary data will be dependent on the accuracy and completeness of the data used. Validity of data should thus be regularly assessed given that it can be influenced by many factors and can change over time.

Moreover, as seen in this thesis, new specialist medicines—particularly orphan medicines and medicines with narrow indications or restricted reimbursement—are used in relatively small patient populations. This may pose methodological challenges in assessing the value of these new medicines in routine clinical practice. Also, the findings indicate that the very first patients receiving a new medicine in routine clinical practice may differ considerably from the patients in the pivotal trials. For example, the first wave of dimethyl fumarate uptake was predominantly due to patients switching from other disease-modifying treatments. While a detailed description of the first olaparib users could not be provided it is possible that they also differed from the trial participants. Finally, when it comes to the assessment of treatment outcomes, a balance needs to be found between allowing for sufficient follow-up time to accrue and providing timely insights to decision makers. If analyses are performed too soon after the introduction then data may not be mature yet. However, if done too late then an opportunity to improve patient outcomes may be missed.

Despite the aforementioned limitations, data collected as part of routine care in Sweden provide unique research opportunities. All persons residing in Sweden have access to healthcare from birth or immigration until death or emigration. Moreover, the existence of a personal identity number assigned to every resident allows for linkage of data across various data sources. This enables a broad range of assessments of the use of new medicines and associated outcomes in routine clinical practice.

Acknowledging that the research opportunities in Sweden are unique, it is perhaps not surprising that the complete population-based overview of drug utilization in multiple sclerosis is the only one of its kind published to date. Similarly, almost five years after the marketing authorization of olaparib, the research presented here provides the only published evidence on the use and outcomes of olaparib in routine clinical practice.

6 CONCLUSIONS

This thesis examined selected elements of the process for managed introduction of new medicines. A complete description and evaluation of the Swedish Horizon Scanning System was performed. This was followed by an assessment of the utility of regional and national data sources in examining the uptake, use, and outcomes of prioritized medicines in key therapeutic areas. Moreover, the impact of treatment recommendations as a tool to facilitate rational use of new medicines was assessed. The conclusions of this thesis are presented below.

/ Regional and national decision makers can rely on the outputs of the Swedish Horizon Scanning System to keep informed about new medicines. The assessment demonstrated that all new medicines were identified and all innovative medicines that went on to have substantial economic impact were assessed prior to their introduction.

/ Assessment of drug utilization in multiple sclerosis was possible because individual-level data on the use of both inpatient and outpatient medicines were recorded in the regional data.

/ Assessment of use and outcomes of the growing number of new specialist medicines, including new cancer treatments, may be impeded by a lack of fit-for-purpose data.

/ Treatment recommendations can influence the uptake and utilization of new medicines used in the specialized care setting.

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APPENDIX