TANDVÅRDS- OCH
LÄKEMEDELSFÖRMÅNSVERKET

Follow-up of cancer pharmaceuticals and other pharmaceuticals via alternative data sources

Dental and Pharmaceutical Benefits Agency, October 2020
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Preface

The Dental and Pharmaceutical Benefits Agency (TLV) was commissioned in the 2019 appropriation directions to continue the follow-up of cancer pharmaceuticals and other pharmaceuticals in clinical practice. The assignment is due to be reported no later than 1 October 2020. TLV's work is a continuation of previous assignments relating to follow-up.

The ability to follow-up on the utilisation of pharmaceuticals and treatment effects is a prerequisite for ensuring TLV is able to contribute to the rapid and equal access to new pharmaceuticals and ensuring as many people as possible have access to treatment. Follow-up is also a prerequisite for being able to ensure that the cost of using a pharmaceutical is reasonable in relation to the benefit, not only in subsidy decisions but also throughout the entirety of a pharmaceutical's life cycle. Health care providers and patients expect access to innovative new pharmaceuticals. Since subsidy applications for these pharmaceuticals often include uncertainties about treatment effects and how the pharmaceutical will be utilised, TLV must be able to carry out high quality follow-up.

This report contains the results from seven pilot studies along with the lessons learned from the work on the pilot studies as well as from TLV's other work to expand the use of data from clinical practice. We also describe where continued work is needed. An in-depth description of the pilot studies is presented in the appendices to this report.

The members of the working group for this report have been Sofie Gustafsson, Daniel Högberg, Pontus Johansson, Johan Pontén, Cecilia Tollin and Anders Viberg.

It would not have been possible for TLV to carry out this work on its own. We therefore wish to thank the other agencies, regions, depositories, academic institutions and private actors that have made these pilot studies possible through their expertise, data and efforts.

Agneta Karlsson
Director General, TLV

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Summary

TLV has been tasked with ensuring that pharmaceutical utilisation is appropriate and that the cost for pharmaceuticals is reasonable over the whole life cycle of the pharmaceutical, and according to the appropriation directions, ensuring that the agency will continue to develop value-based pricing. For this reason, TLV needs improved conditions to follow-up on pharmaceutical utilisation and treatment effects in clinical practice.

Within the scope of this government assignment, TLV has been tasked with follow-up of cancer pharmaceuticals and other pharmaceuticals via alternative data sources. The two main questions that TLV sets out to answer in connection with follow-up of pharmaceuticals are *how* are the pharmaceuticals utilised and *what treatment effects* do the pharmaceuticals have in clinical practice. These are two fundamental questions for TLV, and they have constituted the starting point for establishing a schematic overview model. This model shows what information may be needed to answer the broader questions. In order to demonstrate the challenges and opportunities presented by the follow-up of pharmaceuticals and their effects, seven pilot studies were conducted to shed light on different aspects of data access and analysis methods linked to the two main questions in the schematic overview model.

Generally, national government registers, and above all the health data registers of the National Board of Health and Welfare, constitute the fundamental data sources for TLV. The healthcare sector has a duty to report information to the health data registers, which means that the overall coverage rate is very high. The health data registers are national registers, and it is possible to link different registers, even registers from other public authorities like the Swedish Social Insurance Agency and Statistics Sweden. There is also a structured and transparent process for how data from government registers can be shared with actors that apply for access to data.

Among other things, TLV's work shows that the coverage rate in the Patient Register needs to be increased for certain variables that are central to TLV's work. TLV's work also shows that there is very relevant data in the different regional record systems, but this is not regularly available for analysis and follow-up in national government registers. However, there is potential to improve the availability of data from the different regional record systems in national registers so that it is automatically updated and with increased regularity.

In contrast to data on hospital pharmaceuticals that are missing in the health data registers, the Prescribed Pharmaceutical Register contains detailed data on prescription pharmaceuticals that have been dispensed by prescription at the nation's pharmacies. This information is needed for follow-up of prescription pharmaceuticals. A basic condition for TLV to be able to be able to fully develop

value-based pricing is that TLV can also perform follow-up of hospital pharmaceuticals on the national level via health data registers. The single most important change would therefore be if the Patient Register could also be used for follow-up of hospital pharmaceuticals at the individual level. This information must be available independent of the care delivery level or the occupational category that has administered the pharmaceutical. The National Pharmaceutical Strategy also highlights the importance of better access to information about hospital pharmaceuticals in particular as one of the most urgent challenges that needs to be resolved.

Region Värmland's work in Pilot Study 1 shows that it is possible to automate data reporting for hospital pharmaceuticals from the region's data warehouse to the Patient Register. If several regions can achieve equivalent levels of automation, the potential to perform national follow-up of hospital pharmaceuticals on an individual basis should be improved considerably. In Pilot Study 5, it is also revealed that the reporting of other medical interventions needs to be improved and that data on diagnoses at the time of care need to be indicated with more detailed coding than what is typically done today. In addition, the Patient Register needs to be expanded to include data from visits in specialised outpatient care with providers in occupational categories other than physician. Otherwise, one cannot track the use of pharmaceuticals that have been ordered by physicians but administered to the patient at nurse visits in specialised outpatient care. The current shift towards more and more care being delivered close to home is also increasing the need for national follow-up in health data registers for care provided in primary care.

This requires an ongoing effort to more systematically identify how data from the regions' basic data can be automatically made accessible in the health data registers.

In parallel with the need for more and higher quality data, TLV also needs to identify and evaluate methods for how information on pharmaceutical utilisation and treatment effects in clinical practice can be used as a basis for decision-making. In this effort, an array of methods must be applied and evaluated, as different methodological approaches will be more or less suited to this purpose depending on which question is to be addressed, how available the data is, and in what context the analysis is performed. Pilot Study 7, which concerns the Swedish National Diabetes Register (NDR), shows that when relevant data is available, it is possible to apply available methodologies to evaluate efficacy in clinical practice through observational studies. This pilot study also shows that laboratory data or equivalent measurement values can constitute a central parameter in the follow-up of pharmaceuticals (or medical devices).
In most disease areas, however, access to relevant laboratory data via quality registries is lacking. If it is possible to find ways for the data from the regions' local health and medical care systems to be extracted and processed more regularly to perform national analyses at the individual level, highly favourable conditions are created for the performance of follow-up.

The development of the Patient Register according to TLV's proposed measures should lead to more complete health data registers. This would help create better conditions to achieve the vision outlined in the National Pharmaceutical Strategy for *Correct Use of Medicines to the Benefit of Patient and Society*. The focus areas proposed for 2020–2022 concern challenges such as the introduction of new pharmaceuticals, pharmaceutical follow-up and the generation of knowledge and evidence.

Creating more complete health data registers will mean that opportunities for follow-up will generally improve, which is fully in line with Sweden's life science strategy, which highlights the need to utilise health and medical care data for research and innovation.
It may also become easier to introduce advanced therapy medicinal products (ATMPs) or costly pharmaceutical combinations if the health data registers are more complete. This is due to improved conditions to be able to design payment models or agreements that reduce the cost for use through reimbursements that are calculated using data from the health data registers.

The possibility to process health data at the individual level is a basic precondition for being able to fully develop value-based pricing in order to provide the greatest possible health for the tax money spent. For this purpose, TLV needs to be able to process data from, for example, national health data registers at the individual level. In order to facilitate a more systematic follow-up process, the conditions for the National Board of Health and Welfare to be able to deliver data to TLV also need to be reviewed. In order to tap the tremendous potential that lies in the data contained in the national health data registers, TLV thus needs to be granted constitutional support to be able to handle data from the national health data registers at the individual level.

Terms and concepts

ATMP – Abbreviation for Advanced Therapy Medicinal Products: a pharmaceutical for advanced therapy that can be categorised as gene therapy, somatic cell therapy or tissue-engineered products.

Prescription pharmaceutical – Pharmaceuticals that are prescribed to a patient and dispensed by prescription at a pharmacy.

Health data register– The National Board of Health and Welfare administers a range of health data registers including the Prescribed Pharmaceutical Register, the Patient Register, the Swedish Cancer Register and the Cause of Death Register. The health data registers enable the analysis and monitoring of developments and trends in health care and social services. The health data registers are regulated under the Health Care Data Register Act (1998:543).

Non-randomised study – A non-randomised study is a study where either the intervention that is to be investigated in the study or the alternative intervention is not given to subjects at random. Randomly deciding (randomisation) which participants will try a new pharmaceutical is considered to be an important part of a study in order for the study to be able to demonstrate the efficacy of the new pharmaceutical.

Combination therapy – Combination therapies can contain several pharmaceuticals and are commonly used, for example, in cancer treatment. A combination can contain both procured pharmaceuticals and pharmaceuticals that are included in the high cost protection scheme, and different components in a single combination may be owned by more than one company.

Life sciences – The life sciences contribute to the improved health and quality of life of the population, ensure economic prosperity and develop knowledge. The life sciences sector includes the companies, universities and university colleges as well as public actors at the municipal, regional and state level that contribute to the promotion of public health through their activities. The sector includes research, higher education and innovation, pharmaceutical development and medical devices as well as treatments and prevention, implementation and follow-up.

National quality registry – A national quality registry contains individualised data about patient diagnoses/problems, medical interventions and outcomes after treatment across all modes of health care delivery. There are currently just over 100 national quality registries for different diagnoses or disease areas.

The National Pharmaceutical Strategy (NLS) – the National Pharmaceutical Strategy was adopted by the central government and the Swedish Association of Local Authorities and Regions as the parties to the National Pharmaceutical

Strategy. In Sweden, some thirty public authorities and organisations are active within the strategy.

PROM and PREM – the Abbreviation PROM stands for Patient Reported Outcome Measures and measures functional well-being and health-related quality of life. PREM stands for Patient Reported Experience Measures and measure the patient's experience of and satisfaction with care.

Hospital pharmaceuticals – Pharmaceuticals that are procured by the health care providers and administered directly to the patient during the delivery of care.

RWD – Abbreviation for Real World Data, which describes data about the effect of pharmaceuticals that does not come from clinical studies, for example, but from other sources, such as the patient and the health care provider.

The Council for Knowledge Management – the Council for Knowledge Management, which is governed by an ordinance (2015:155), deals with strategically important issues that contribute to ensuring that the right knowledge reaches principals and professionals working in health care and the social services. Nine government agencies are included in the council, and the National Board of Health and Welfare's Director General is the chairperson.

Surrogate measures – Measurable factors that are related to patient outcomes to some extent and are relevant for the patient. Examples of surrogate measurements in health and medical care are blood lipids, blood pressure and bone density.

1 Introduction

1.1 Background

1.1.1 TLV's assignment

According to the agency's instructions, TLV shall contribute to the efficient and cost effective use of pharmaceuticals in health care and ensure the general population has good access to these pharmaceuticals in accordance with the ethical principles for priorities in health care. Under the assignment, TLV shall also contribute to the rapid and equal access to new pharmaceuticals and help to ensure that as many people as possible have access to treatment. This must also be balanced against the notion that utilisation should be cost effective, not only when deciding on a subsidy but also during the whole life cycle of a pharmaceutical.

To be able to ensure that pharmaceutical utilisation is efficient and cost-effective over time, in its appropriation directions, TLV has been tasked with developing value-based pricing. To this end, TLV needs improved conditions to follow-up on utilisation and efficacy in clinical practice.

Further, in its appropriation directions, TLV has been tasked with promoting innovation by facilitating the use of new, innovative and cost-effective pharmaceuticals.

In the appropriation directions for 2019 (S2019/04860/FS), the government tasked TLV with continuing the assignment to follow-up on cancer pharmaceuticals and other pharmaceuticals in clinical practice. Under the assignment, TLV shall investigate the possibility of using alternative data sources linked to the health care sector's basic data for different types of follow-up, for example, by extracting data from medical records.

1.1.2 Need for follow-up of new pharmaceuticals

For new pharmaceuticals where introduction to the market is characterised by uncertainty around clinical efficacy and how the pharmaceutical will be utilised in clinical practice, it can be difficult for payers and authorities who are tasked with evaluating the pharmaceutical to determine whether the cost is reasonable in relation to the benefit that the treatment provides. These types of uncertainties are common for pharmaceuticals used in cancer treatment, but they are also common for many orphan pharmaceuticals, precision medicines and new so-called advanced therapy medicinal products (ATMPs).

In these areas, new pharmaceuticals are sometimes approved in the early stages of development. In these cases, approval is often based on surrogate markers, i.e. measurable factors that are assumed to correlate with real clinical outcomes that are relevant for the treatment, or results from non-randomised studies. Such new

pharmaceuticals are often associated with high costs and a high degree of uncertainty about clinical efficacy over the longer term, but they also have the potential to be highly beneficial. The ambition behind early approval is to provide quick access to treatments that appear promising, especially for patients who do not currently have access to any treatment options. On the other hand, early approval increases uncertainty around whether the use of the treatment in clinical practice actually corresponds to the presumed benefit at the time a subsidy decision was made.

An individual pharmaceutical often holds marketing authorisations for several treatment indications, which means that an individual pharmaceutical may be used for the treatment of several different diseases. However, TLV's subsidy decision may need to be limited to only include one or a few of the approved indications. Because TLV must be able to ensure that the pharmaceutical is used at a reasonable cost, it must be possible to follow up on the subsidy limits. Many cancer pharmaceuticals are used in combinations or in sequences, where pharmaceuticals covered under the pharmaceutical benefits scheme and hospital pharmaceuticals are both included. The subsidy for a pharmaceutical may be limited to after the patients have tried another pharmaceutical, which may be a hospital pharmaceutical. Since it is not possible to follow-up on an individual's utilisation of hospital pharmaceuticals on the national level, it is not always possible to follow-up on whether the limitation for the subsidy is observed. This makes it difficult for TLV to ensure that pharmaceuticals given under the pharmaceutical benefits scheme are used at a reasonable cost.

New pharmaceuticals are often associated with medical and economic uncertainties. Side agreements that have been concluded between regions and companies for certain pharmaceuticals since 2015 represent one tool to manage such risks. Increased possibilities to perform follow-up of pharmaceutical utilisation opens the door to greater opportunities for relevant side agreements to be reached that are adapted to the specific conditions for each individual pharmaceutical.

When patients are to be treated for cancer, for example, it can be medically justified to combine several new pharmaceuticals in a combination therapy. High pharmaceutical costs, however, can mean that care providers are restricted in the use of such combination therapies. TLV has worked with the regions and a pharmaceutical company to implement a project that intends to reduce the cost for pharmaceuticals included in a particular combination therapy. Despite the fact that the regions and the company in the project were able to agree on a payment model, an agreement could not be signed. This was due to the fact that formulation of the agreement required access to national follow-up data for hospital pharmaceuticals at the individual level, which is not currently available in the national registers.

1.1.3 Need for follow up of *established pharmaceuticals*

In April 2020, TLV submitted the report *Översyn av besparingspotentialen för läkemedel* (*Review of the savings potential for pharmaceuticals*) to the government. The report shows that pharmaceuticals that have been included under the pharmaceutical benefits scheme between five to ten years have a slightly higher

price profile in Sweden than in other EU countries. There is a potential for savings within this group of pharmaceuticals. But in order to be able to more precisely identify a potential source of savings, one also needs to be able to identify the reason for the prescription and other patient characteristics as well as health outcomes for the treatments. Otherwise, it can be difficult to achieve savings without creating a risk that companies will choose to withdraw pharmaceuticals from the pharmaceutical benefit scheme. One conclusion in the report is that side agreements represent an important tool in reassessments to ensure a reasonable cost for a pharmaceutical throughout the entire life cycle and to realise potential savings, without compromising the availability of necessary pharmaceutical treatments.

1.1.4 Experience from previous work

Data availability is crucial for follow-up of pharmaceuticals and their treatment effects. Availability is dependent on data that is found in medical records, from the actual patient and the data that is regularly reported to the register. Data availability is also dependent on the ability to link data from different sources in order to be able to benefit from the information that is available. This may relate to data from national registers of medicines, health data from the National Board of Health and Welfare, quality registers, regional administrative systems, but also data from the Swedish Social Insurance Agency and Statistics Sweden (SCB). Furthermore, competence must be developed to be able to determine which analysis methods are suitable in evaluating data from clinical practice. With better access to relevant data and analysis methods, opportunities to perform follow-up of the utilisation of pharmaceuticals and treatment effects increase, thereby creating the conditions to ensure that pharmaceutical costs are reasonable given the uncertainties that exist.

TLV needs to continuously perform follow-up of pharmaceutical utilisation and treatment effects in clinical practice. This means that TLV needs access to timely data from national registers at the individual level. The agency also needs to be able to use data that are found in different health care systems.

Questions concerning data availability and methods are complex and require continuous work to develop the data. In the appropriation directions for 2017, TLV was tasked with two assignments, which were jointly reported in a single report to the government in December 2018. One assignment tasked TLV with carrying out two pilot studies on treatment effects in clinical practice. In the second assignment, TLV was tasked with working in consultation with the Swedish Association of Local Authorities and Regions to carry out a pilot study with the aim of developing a quality register for follow-up of pharmaceutical utilisation in cancer treatment at the national level. Within the scope of the assignments, TLV carried out three additional pilots with a focus on the collection and analysis of data for follow-up of pharmaceutical utilisation.

TLV has previously determined that access to data at the right time is an important cornerstone for performing follow-up of pharmaceutical utilisation and treatment effects in clinical practice and that the availability of data needs to be improved.

TLV also notes that collaboration with other actors, such as actors in academia, other agencies and the regions, is important for developing opportunities for follow-up. Among these actors, the common need is to find ways to adapt the data that is extracted so that it is timely, structured and can be analysed and thus can be used to develop methods for evaluation or follow-up of pharmaceutical effects.

1.2 Starting point and schematic model

In its work on *Follow-up of cancer pharmaceuticals and other pharmaceuticals via alternative data sources*, TLV proceeds based on the assumption that it is a continuation of the previous assignment to perform follow-up of cancer pharmaceuticals and other pharmaceuticals in clinical practice. The work is based on the conclusions the agency arrived at in its earlier report within the scope of the agency's follow-up assignment.

Under the current assignment, TLV shall investigate the possibility of using alternative data sources linked to the health care sector's basic data for different types of follow-up, for example, by extracting data from medical records. The goal of the agency's work is to create alternative approaches in situations where data from randomised clinical trials cannot be used as a reference or when relevant data are not available in national or regional quality registers.

TLV has carried out its work in seven pilot studies. The pilot studies are partly directed at identifying data gaps and proposing alternative approaches for follow-up, and partly to show that in situations where relevant data is available, there are analytical methods for follow-up of pharmaceutical utilisation and effects in clinical practice. The agency's work also shows that data on pharmaceutical utilisation can be important information to apply in subsidy decisions, especially in reassessments.

1.2.1 Schematic model of relevant questions and variables

Essentially, TLV strives to use Real World Data (RWD) to answer two main questions: How is the pharmaceutical utilised, and what effect does the pharmaceutical have on health outcomes in clinical practice? The question of how the pharmaceutical is utilised can be divided into two categories: pharmaceutical-specific or patient-specific questions. Pharmaceutical-specific questions are, for example, what indication(s) the pharmaceutical is used for, how the pharmaceutical is dosed, treatment duration, treatment in combination with other pharmaceuticals and adherence to pharmaceutical treatment. The patient-specific questions concern, for example, the patient's previous treatments, the patient's health status and any comorbidities. Sex, age and socio-economic conditions can also be important patient-specific factors.

TLV has developed a schematic model in order to illustrate the main questions that need to be answered and the variables that may be needed to answer these questions. The model can be found in Figure 1.

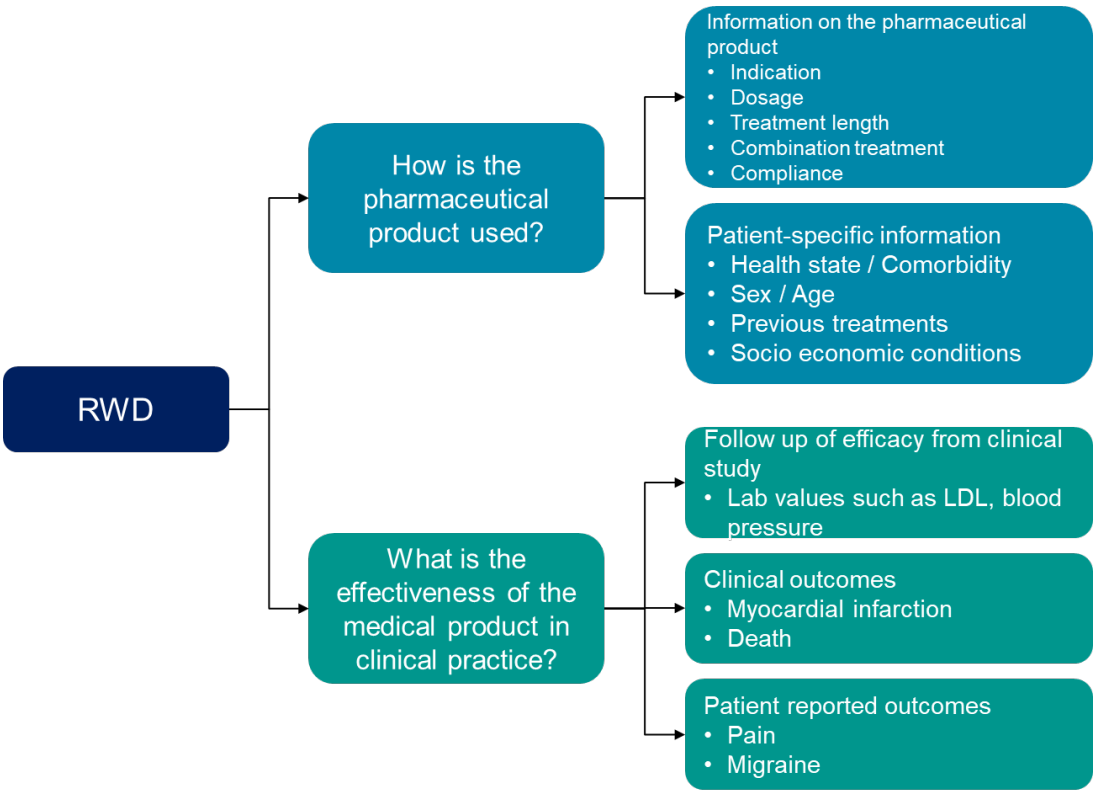

Figure 1. Schematic model of the main questions TLV strives to answer with RWD and examples of variables that may be needed to answer questions about pharmaceutical utilisation and treatment effects in clinical practice.

TLV is able to perform follow-up of pharmaceuticals that are dispensed by prescription in pharmacies, and certain questions about how the pharmaceutical is used can be answered using data from the Prescribed Pharmaceutical Register and the Patient Register. However, the agency is not able to perform national follow-up of hospital pharmaceuticals on the individual level. When the National Medicines List is introduced, it will contain information on the reason for the prescription.

Studying the health effects of a pharmaceutical in clinical practice requires more information than how the pharmaceutical is used; it also requires information on how the individual's health is changed over time. The National Board of Health and Welfare's Patient Register contains data on diagnoses at the time of care as well as interventions in inpatient care and at doctor's visits in specialised outpatient care. The data from the Patient Register can be used to track overall changes in health over time, which is a precondition for being able to follow-up treatment effects in clinical practice. The Patient Register and the Prescribed Pharmaceutical Register are updated monthly, which makes them more relevant for TLV's follow-up work than any of the other health data registers maintained by the National Board of Health and Welfare.

Health-related outcome measures that may be relevant to examine with respect to pharmaceutical effects can be, for example, severe clinical outcome measures such

as myocardial infarction or death. These data are often available in the Patient Register and the Cause of Death register but often require long follow-up studies. Other outcome measures can be the measures used in the underlying clinical study, which are sometimes surrogate measurements. These can be, for example, laboratory values such as LDL, which indicates cholesterol levels in the blood or other values such as blood pressure. Data about laboratory values and equivalent measured values are not available in the health data registers.

1.2.2 Choice of methodology and pilot studies in the assignment

Below, the seven pilot studies conducted by TLV are described along with the reason they were selected.

Pilot studies 1-4 highlight different aspects connected to questions about pharmaceutical utilisation in clinical practice, where Pilot study 1 and Pilot study 3 propose alternative procedures for follow-up in situations where relevant data is not available in the national registers. Pilot study 2 shows that information about how pharmaceuticals are used can help form the basis for subsidy decisions. Pilot study 4 shows that disease severity at the group level can differ between patients that obtain early or late access to a new pharmaceutical. Such a change in pharmaceutical utilisation over time can be relevant in the choice of analytical method during efficacy studies.

In pilot studies 5-7, it is demonstrated that the health data registers can potentially be used for follow-up of treatment effects and that in situations where relevant data can be obtained, there are also methods for follow-up of treatment effects in clinical practice.

The work in this report has been carried out in collaboration with actors in academia or other actors. External actors are responsible for their respective pilot studies and are responsible for the results that are presented in the appendices to this report. However, TLV is solely responsible for other contents in the report and the analyses, conclusions in the report, and the proposals that are presented in sections 3 and 4.

As described above, there are currently no opportunities for national follow-up of hospital pharmaceuticals at the individual level, which limits the opportunity to perform comprehensive follow-up of pharmaceutical utilisation. Pilot study 1 shows that it is possible to improve opportunities for follow-up via the Patient Register. In the pilot study, Region Värmland worked to implement the automatic transfer of data to the Patient Register for pharmaceuticals administered to patients in inpatient care or at doctor’s visits in specialised outpatient care.

Pilot study 2, which was focused on pharmaceuticals used in haemophilia, is an example based on TLV’s own activities and shows the potential to use data on pharmaceutical utilisation from the Prescribed Pharmaceutical Register to support decision-making in the reassessment of pharmaceutical subsidies.

Pilot study 3 illustrates how patients can contribute patient-reported data in a structured format that can be used for follow-up of pharmaceuticals over the long term. The concept is demonstrated in a pilot study that has been carried out in a collaboration between TLV and the company Upstream Dream. Physicians typically prescribe multiple antibiotics to patients with cystic fibrosis so that they can begin a course of treatment quickly when necessary. The pilot study shows that by using a mobile phone application, which is designed specifically for patients with cystic fibrosis and is classified as a medical device, patients can more easily keep track of, for example, when a course of antibiotics is started. The patient enters information in the app about when the treatment is started. The patient is able to share the information with the health care provider and can also give consent for the data to be sent to a quality register. The ability to collect patient-reported data as structured data to, for example, measure outcomes and effects, may mean that in the long run this type of data can be used more regularly in follow-up of pharmaceutical utilisation and treatment effects in clinical practice.

Pilot study 4 is a continuation of a pilot study that was reported in the government assignment from 2018. The pilot concerns treatment with both the PCSK-9 inhibitors Repatha and Praluent as well as the chronic heart failure pharmaceutical Entresto. A problem that was previously identified was that if the characteristics of the patient population that are started on any of the pharmaceuticals vary at different points in time after the introduction of the pharmaceutical, it may affect how follow-up of the pharmaceuticals' effect should be designed. This could lead to a situation where the comparison alternative needs to be different for the patients who are prioritised to try the pharmaceutical when it is first available, compared with those who start a treatment later. In order to obtain more in-depth knowledge in this area, TLV proceeded with a pilot study that evaluates the possibility of using national health data registers. The aim was to investigate whether the population of patients newly started on a pharmaceutical is different at different points in time. The study has been carried out in collaboration with Uppsala University.

Pilot study 5 is a study that uses data exclusively from the National Board of Health and Welfare's health data registers to follow-up on, for example, differences in treatment effects between the cancer pharmaceuticals Xtandi and Zytiga. The study has been carried out in collaboration with Gothenburg University and has been underway for one year. The study also includes a review of the usability of relevant variables in the National Board of Health and Welfare's health data registers in terms of the ability to answer questions about what type of data access and what level of data quality is needed.

Pilot study 6 is a study that uses data from the National Board of Health and Welfare's health data registers combined with data from interviews with prescribers to perform follow-up of treatment effects for the cancer pharmaceuticals Xtandi and Zytiga. Since this pilot study runs for several years, an interim report with a focus on study design is provided in this report. The study is being carried out in collaboration with Uppsala University and has been underway for three years. In-depth interviews are used to create the conditions needed to identify the background variables that guide a physician to prescribe the respective

pharmaceuticals. This makes it possible to ensure that these variables are included in the analysis, so that comparable groups can be formed that allow for the evaluation of two different treatments against each other.

Pilot study 7 builds on one of the studies included in the government report *Follow-up of pharmaceutical utilisation and treatment effects in clinical practice,* which TLV submitted to the government in 2018. The study in the previous report uses data from the Swedish National Diabetes Register (NDR) to evaluate whether patients in clinical practice who have been treated with diabetes pharmaceuticals and have characteristics that would have met the eligibility criteria in the clinical study, also have treatment results that are consistent with the results of the clinical studies. In collaboration with the Swedish National Diabetes Register (NDR), Pilot study 7 evaluates the external validity of the clinical trials by investigating whether the patients that do not meet the eligibility criteria receive the same effect as those who meet the criteria. The pilot study sets out to examine how machine learning (ML) can be used to evaluate treatment effects in clinical practice.

2 Pilot studies under the scope of the assignment

In order complete its assignment, TLV has carried out seven pilot studies. The pilot studies have been carried out by TLV and in collaboration with external partners. The purpose of the pilot studies is twofold: to evaluate what can already be implemented today with the data sources and methods that are available and to identify what needs to be developed to improve conditions for follow-up and evaluation of pharmaceuticals and their effects in clinical practice.

Pilot studies 1–4 are designed to describe how pharmaceuticals are utilised in clinical practice while pilot studies 5–7 address questions relating to how treatment effects can be evaluated in clinical practice.

2.1 Pilot study 1:

Purpose: To automate the reporting of data on administered hospital pharmaceuticals in inpatient care and during doctor visits in specialised outpatient care from Region Värmland's data warehouse to the Patient Register.
The starting points for the pilot study were that data transfer would occur automatically without placing additional burdens on health care providers and that the project method must be applicable to other regions.
The pilot study was carried out in view of the fact that the reporting of data to the Patient Register on administered hospital pharmaceuticals is low across all regions. The low rate of reporting means that at the national level, there is a lack of basic knowledge about how hospital pharmaceuticals are used at the individual level in inpatient care and in specialised outpatient care.

Data sources: Information about pharmaceuticals that have been administered to patients in inpatient care or at doctor's visits in specialised outpatient care was identified in Region Värmland's data warehouse. Data of interest came from the healthcare systems Cosmic and CytoBase.

Implemented by: Region Värmland and TLV with support from Amilliant AB**.**

Method: The project includes the creation of an automatic transfer method for data from medical records in Journalia's healthcare system, Cytobase, to Region Värmland's data warehouse in the healthcare system Cosmic. The Cytobase data is then linked to medical record data in Cosmic and information on all pharmaceuticals at the ATC level is automatically transferred from the region's data warehouse to the National Board of Health and Welfare.

Results: Region Värmland runs an automatic monthly export from data warehouses to The National Board of Health and Welfare's Patient Register. The

export includes information from Cytobase on pharmaceuticals administered in the treatment of cancer and information from the Cosmic Intelligence BI module on other pharmaceuticals that have been administered within inpatient care or by a physician in specialised outpatient care. In addition to information on pharmaceuticals on the active substance level (seven-digit ATC codes), data on personal identity numbers, hospital and admission/discharge dates is exported. Region Värmland exported the first data set to The National Board of Health and Welfare in May 2020; thereafter, data is exported monthly.

After the first data transfer, TLV ordered statistics from The National Board of Health and Welfare's Patient Register for eight different pharmaceutical substances. The statistics were used to verify that data from Region Värmland have been entered the Patient Register. The three-month period from February to April 2020 was compared with the period from November 2019 to January 2020 to evaluate if there were any differences in the number of patients. Figure 2 shows a marked increase in the number of patients who have been reported to have had pharmaceuticals administered as an activity during the delivery of health care. The substances include cancer pharmaceuticals (daratumumab and paclitaxel), which makes it possible to confirm that information from Cytobase has also been transferred.

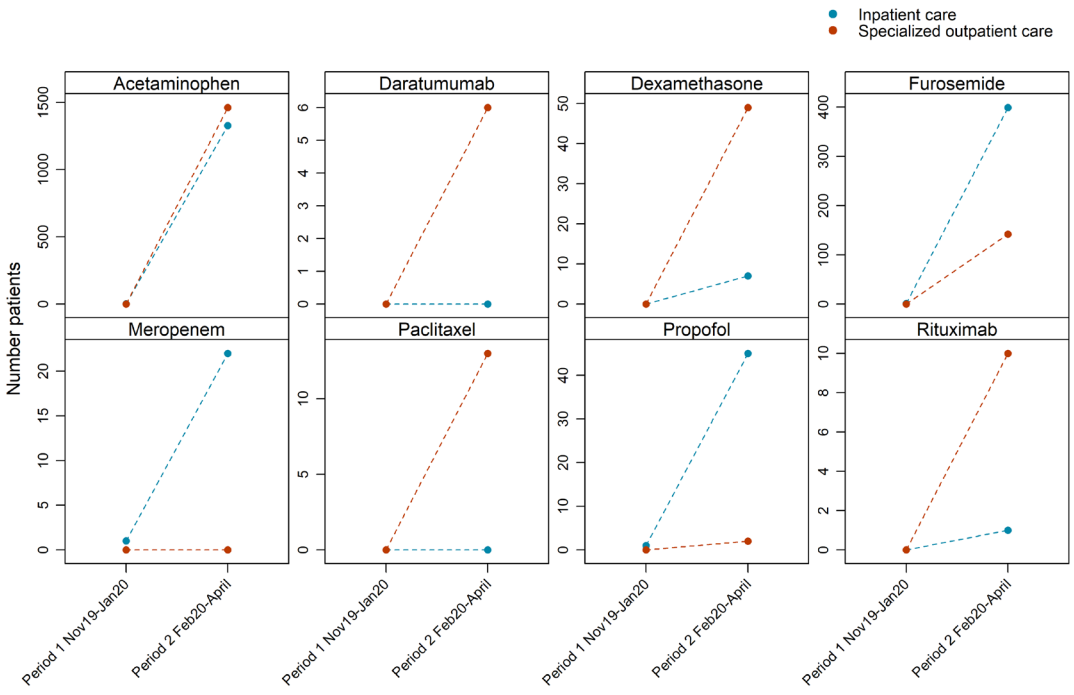

Figure 2. Number of patients in Region Värmland in the Patient Register with a reported use of eight different pharmaceutical substances.

Figure 3 shows reporting for all regions to the Patient Register on the use of paracetamol, which is one of the most frequently used substances in specialised care, for the same time periods as above and in the same way. The number of

patients in regions other than Region Värmland who have been reported to have used paracetamol is negligible, which indicates that there is a lot of room for improvement.

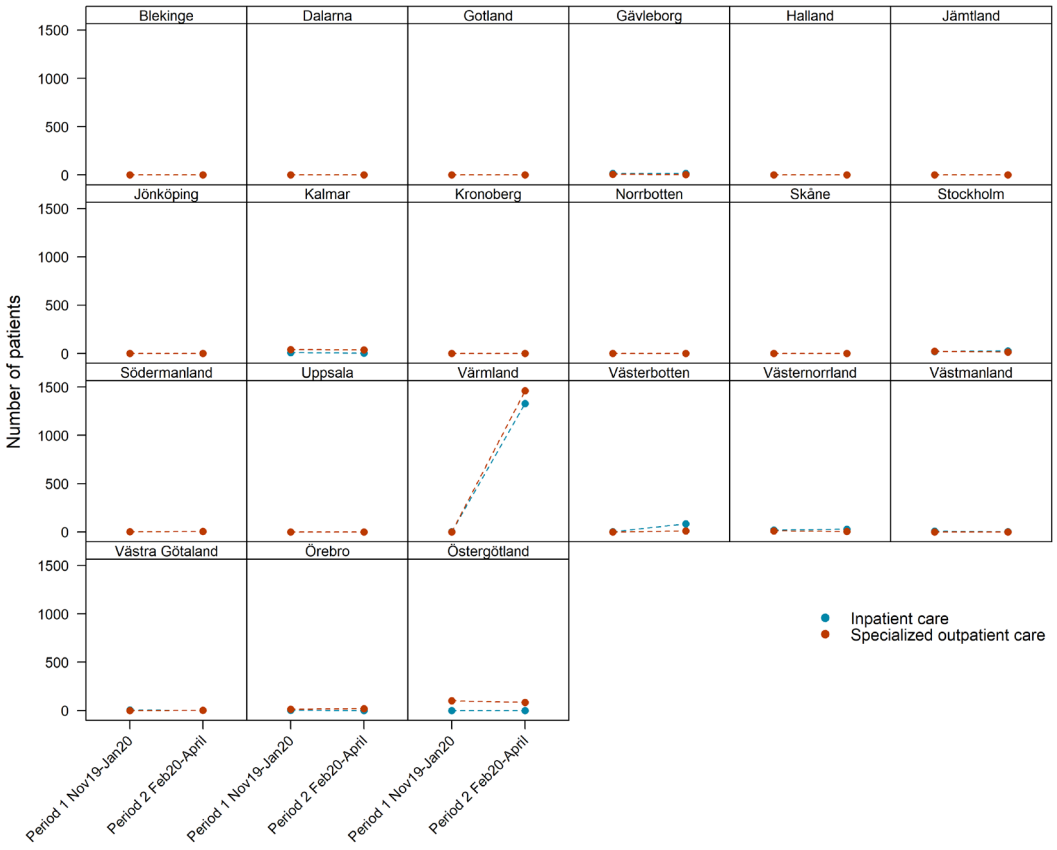

Figure 3. Number of patients in the Patient Register with reported use of paracetamol by region.

Other experience: The pilot study conducted with Region Värmland shows that it is possible to establish the automatic transfer of data on pharmaceuticals (ATC code level) administered in inpatient care and at doctor's visits in it specialised outpatient care without increasing the administrative burden on health care providers. The starting point for the pilot was that the project methodology, with some adjustments, could ultimately be used to scale up automated data transfer to the Patient Register for the entire Cosmic customer group (Västmanland, Uppsala, Jämtland/Härjedalen, Östergötland, Kalmar, Jönköping, Kronoberg and Capio). TLV assesses that this should also be possible for other regions.

The transfer of data on hospital pharmaceuticals to the Patient Register needs continued verification in a number of ways. One effective way, as mentioned above, is to expand reporting to more regions. In addition to continuing the work of exploring the possibilities to transfer data on hospital pharmaceuticals to the Patient Register, the possibilities of automating the transfer of more detailed data to the Prescribed Pharmaceutical Register can simultaneously be investigated.

2.2 Pilot study 2:

Purpose: To evaluate the use of prophylaxis treatment for haemophilia. Haemophilia is a disorder where the blood does not clot normally, which a necessary process to stop bleeding. In patients with haemophilia A, there is a deficiency of clotting factor VIII, and in haemophilia B, there is no clotting factor IX. Patients therefore receive factor concentrate as a treatment. Certain concentrates have a longer half-life than others, and in previous decisions, TLV has therefore assumed that this has led to lower consumption levels for these concentrates compared with the corresponding concentrate without an extended half-life. To evaluate whether this assumption is in fact true, TLV has analysed data from the Prescribed Pharmaceuticals Register in connection with reassessments of factor VIII and IX concentrates (reg. nos. 00123/2020 and 00666/2020, respectively).

Data sources: The National Board of Health and Welfare health data registers: Prescribed Pharmaceutical Register

Implemented by: TLV

Method: Patients with haemophilia A who switched from a concentrate with a normal half-life to either Adynovi or Elocta, which have a longer half-life, were evaluated. Patients with haemophilia B who switched from a concentrate with a normal half-life to either Alprolix or Refixia were evaluated. The patients were identified via the Prescribed Pharmaceutical register, after which the total of the factor VIII or factor IX concentrate dispensed to the individual patient the year before a change was compared with the total dispensed the year after a change. The assumption was that patients would be dispensed less of the pharmaceuticals with an extended half-life, which would justify the fact that these pharmaceuticals can have a higher price per unit. Sensitivity analyses were performed to ensure that the results were not due to a situation where, for example, patients collect extra medication when changing in order to have a buffer at home or that patients weigh more as they get older and therefore need more factor concentrate, which leads to increased dispensation over time.

Results: The analysis shows that patients who switch to Adynovi or Elocta (Figure 4) do not have lower dispensed amounts of factor VIII concentrate than before the switch. Patients who switched to Alprolix or Refixia (Figure 5), on the other hand, have lower dispensed amounts of factor IX concentrate than before they switched. In recent decisions, this has led TLV to assess that the annual consumption of Adynovi and Elocta is the same as factor VIII concentrate without an extended half-life. For the factor IX concentrates with an extended half-life (Alprolix and Refixia), TLV assessed that they require a lower annual consumption and that a higher price could thus be justified.

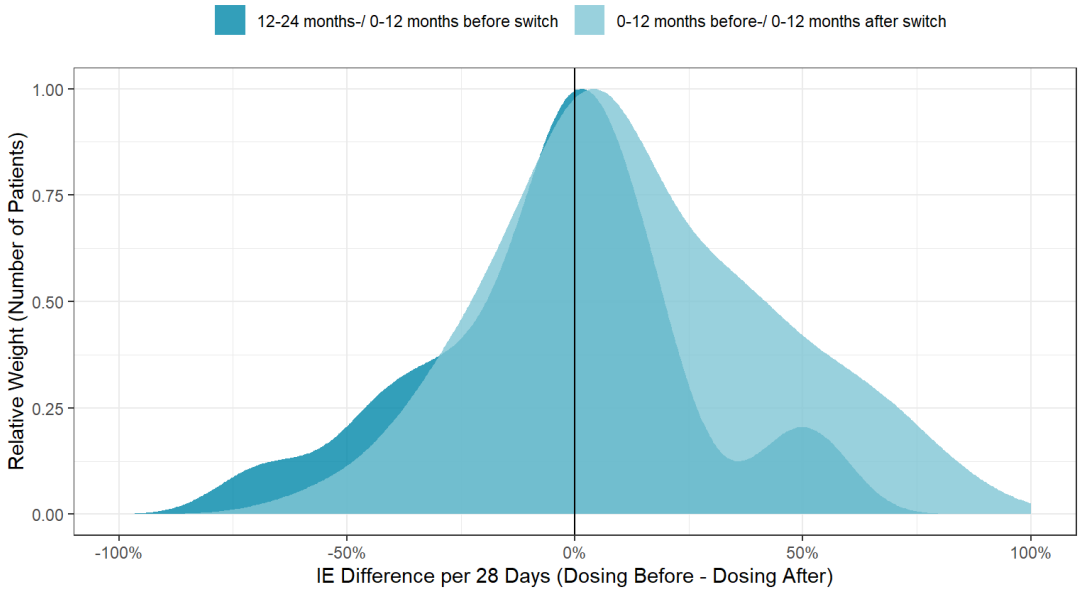

Figure 4. Relative difference in the dispensed amount of active substance for factor VIII preparations in the period 12 months before and 12 months after switching to Elocta or Adynovi. The corresponding relative difference for 12-24 months before and 0-12 months before the switch is shown in dark blue.

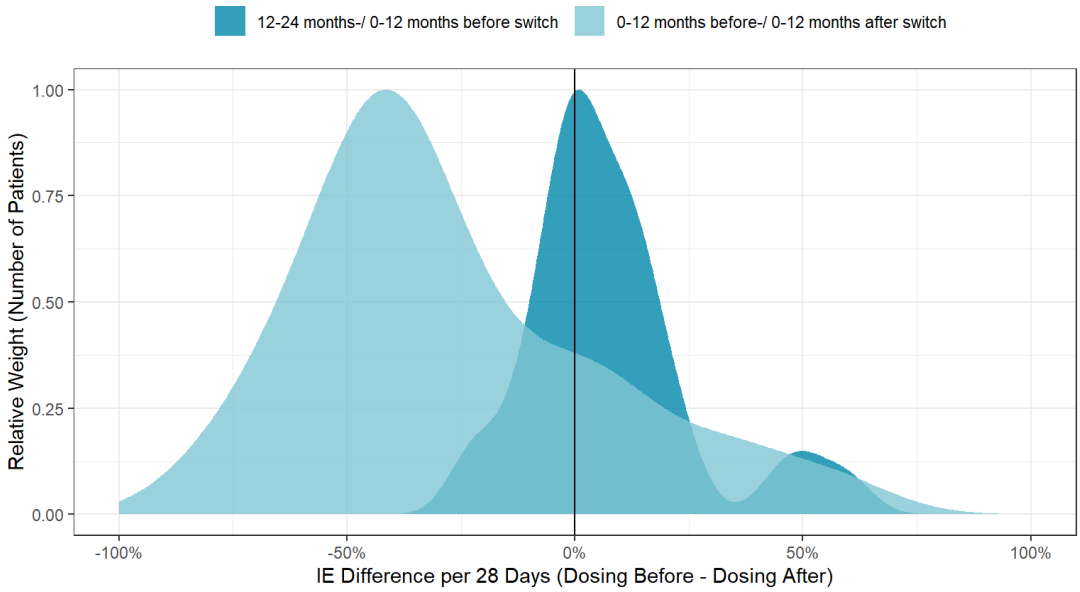

Figure 5. Relative difference in the dispensed amount of active substance for factor XI preparations in the period 12 months before and 12 months after switching to Alprolix or Refixia. The corresponding relative difference for 12-24 months before and 12 months before the switch is shown in dark blue.

Other experience: This analysis was done in connection with the reassessment of all factor VIII concentrates and factor IX concentrates and was part of the basis used for subsidy decisions.

2.3 Pilot study 3:

Purpose: Follow-up of antibiotic use for cystic fibrosis using patient-reported data collected through a mobile telephone application. The purpose of the pilot is to investigate the conditions for patients with cystic fibrosis to have access to information about dispensation of their antibiotics at pharmacies. The information can also be shared among care providers and reported to registers where data can be linked to other reported data and used for further analyses of, for example, care utilisation and treatment effects.

Data sources: Patient-reported data and the Medicine Check E-service of the e-Health Authority.

Implemented by: Upstream Dream AB

Method: Patients with cystic fibrosis are often treated with antibiotics. The patients often have medications in the home and a course of antibiotics can often be started in consultation with a prescriber. Many patients use the Genia application to share information with their prescriber and manage data relating to their illness. It is the patient's own app, but at the same time, it is classified as a medical device. The pilot study aimed to evaluate the legal and practical possibilities that patients could receive information from the eHealth Authority digitally about which medications have been dispensed to the patient at the pharmacy. The patient can then import this information to Genia. When the patient begins a new course of antibiotics, it can then be entered in the app and the patient can choose to share information from a trusted third party (the eHealth Authority) with their health care provider or a register. Since data on when the patient is dispensed antibiotics may not correspond to the date the course of treatment actually begins, the patient's self-reported data may create a more accurate picture of the occurrence of infection. By allowing the patient to choose to share this information, the patient can contribute data that would otherwise not be available.

Results: The pilot was based on the idea that the supplier of the technical application Genia would act as a group representative for the patient and thereby gain access to the patient's dispensation history. It was determined that this would require new legal and technical capabilities on the part of the eHealth Authority. An alternative approach was chosen where the individual patient could access his/her own information at the eHealth Authority via the same database services used by the Medicine Check E-service. This information is currently not available for download or import. A dialogue has therefore been initiated with the eHealth Authority to determine what needs to happen for this information to be available digitally. The advantage of using a technical application for the digital transfer is that the app supplier is the party who acts as the information security officer and personal data controller under the framework of the GDPR.

In order to expand the testing of the concept and evaluate the pilot studies, trials were performed where patients manually transferred data on dispensed antibiotics and the date treatment was started by entering this information in the app. The

patient can choose to export the data to the health care provider, who can then use the information when delivering care to the patient. Data can thereby also be transferred to a national quality register.

Other experiences: The pilot study shows that there is a potential to use the patient as a data source. It is only the patient that has information about when he/she actually starts a treatment. When the patient shares this information with their various health care providers and/or a register, information that only the patient has access to can be used to evaluate the patient's state of health when the patient meets with his/her care provider, but it can also be used as information for follow-up of a patient group. It is possible for patients to manually enter information about dispensed pharmaceuticals into Genia, but in order to simplify this process and ensure high levels of fidelity, it would be preferable to have an automatic transfer of data directly into Genia. It also increases data quality and confidence in patient reported outcome measures (so-called PROMs).

The interim report is available in its entirety here

2.4 Pilot study 4:

Purpose: Evaluation of the change in population of patients treated with Entresto or PCSK9 inhibitors. Within the scope of the government assignment Follow-up of pharmaceutical utilisation and treatment effects in clinical practice, (reg. no. 03381/2018), the effect of both Entresto (a combination of sacubitril and valsartan) and so-called PCSK9 inhibitors was studied. For the PCSK9 inhibitor, a difference in effect over time was observed. There can be a variety of reasons for this result, for example, that sicker patients get access to the pharmaceutical first and patients who are not as sick receive treatment a while after the introduction of each pharmaceutical on the market or that providers initially avoid treating sicker patients due to concerns about side effects that may not be completely identified shortly after introduction. This could, of course, affect the probability that a patient can achieve the outcome that is measured as an effect for the pharmaceutical. Whether patients are more or less likely to have this outcome has nothing to do with the pharmaceuticals themselves but is a consequence of the morbidity of the patient group and the fact that this can change over time. The purpose of this pilot study is to investigate how the patient population changes over time and to contribute to the body of knowledge about how follow-up studies should be designed to accurately evaluate therapies. Within the pilot, Entresto and the PCSK9 inhibitors Repatha and Praluent are studied and a literature review of registry studies is conducted to shed light on how many published studies use methods to address the selection of factors that are not known or cannot be observed in the data and that could affect outcomes.

Data sources: The National Board of Health and Welfare health data registers: The National Patient Register and the Prescribed Pharmaceutical Register

Implemented by: Uppsala University

Method: In order to obtain a dataset of characteristics for the individuals who initiated treatment with either Entresto or one of the two PCSK9 inhibitors, the Patient Register and Prescribed Pharmaceutical register were referenced. For each individual, age, sex, number of days in inpatient care are noted, as well as different diagnostic codes for 5 years, before starting any of the different pharmaceutical treatments. Entresto patients are grouped to those who start treatment before 2018 or during 2018. Patients receiving PCSK9 inhibitors are grouped to those who start treatment in 2016 or 2017 and later. A comparison is then performed to determine whether those who start either treatment during the earlier or later period differ in relation to these underlying factors.

Results: For Entresto, it was found that older patients were treated in 2018 and that these patients have fewer inpatient episodes for different heart diagnoses and more right-side heart failure in the years before treatment compared with the other group. The individuals prescribed PCSK9 inhibitors in 2016 have, on average, a higher rate of inpatient admissions with a diagnosis of coronary heart disease, cerebrovascular disease, implants and grafts in the heart and vessels and lipid disorders in the 5-year period before starting treatment, compared to those starting treatment in 2017 –2018. The differences observed between groups does not necessarily affect outcomes, but there is good reason to at least consider these differences when evaluating the effect of any of these pharmaceuticals. If the group that is newly started on a treatment changes sufficiently, this may lead to the need to change the comparator alternative. An alternative to the treatment may potentially be used for the first few years then changed to another alternative.

Other experiences: The literature study shows that there are very few examples of follow-up studies of treatment effects in clinical practice that have been done using methods that adjust for selection based on unobservable factors (e.g. instrumental variables analysis, regression discontinuity, or difference-in-differences). In order to evaluate the pharmaceutical effect in clinical practice, it may be relevant to further investigate how and when these methods can be used.

The interim report is available in its entirety here

2.5 Pilot study 5:

Purpose: Follow-up of prostate cancer treatment with data from national health data registers. The study aims to examine the usability of the National Board of Health and Welfare's health data registers in the analysis of pharmaceutical treatment effects. Prostate cancer, and more specifically the pharmaceuticals Xtandi and Zytiga, was chosen to illustrate usability. In the pilot, usability is analysed across three dimensions: (1) principal access to information that enables the study of treatment effects (provided by the set of variables in each register), (2) the practical access to the same information (missing data), and (3) administrative costs for data collection, interpretation, coding and quality control.

Data sources: The National Board of Health and Welfare health data registers: the Swedish Cancer Register, the Prescribed Pharmaceutical Register and the National Patient Register

Implemented by: University of Gothenburg

Method: Within the framework of the pilot study, individual data from four of the National Board of Health and Welfare's health data registers are used. The possibilities of studying the treatment effects of pharmaceuticals in everyday clinical practice were analysed based on this data set. In order to determine the usability of the above-mentioned register data, three sub-studies were conducted to estimate the treatment effect of the two specific pharmaceuticals. The general analysis of the usability of register data looks at, for example, the register information available *in practice* and highlights potential, significant discrepancies between this and the basic access to information, as well as the type of empirical analyses that can be performed in principle or in practice. It is well-known, for example, that different variables in the registers have missing data. The purpose of this study was to reveal the extent to which this missing data presented obstacles to the determination of the treatment effect of pharmaceuticals in clinical practice.

Register information was retrieved for a population that was identified as having prostate cancer in the Swedish Cancer Register. The aim of the study is therefore to use the limited information retrieved to identify both opportunities and problems as well as gaps in the available register information when it comes to determining treatment effects in all disease areas.

Results: It is possible to use the information in the National Board of Health and Welfare's health data registers to analyse the treatment effect of a pharmaceutical. However, there is often lag time in the reporting of data to the registers, which means that data taken from the registers to be used in analysis may not include the most recent treatments.

The administrative costs associated with the collection of information from the registers are significant for the health care sector in that the process creates additional work. Additionally, the costs for processing data are sometimes significant.

There is a significant amount of missing information in the registers, not least data on administered pharmaceuticals in inpatient care and during doctor visits in specialised outpatient care, as well as for other interventions. This missing data makes it difficult, or sometimes even impossible, to perform treatment effect analyses based on this data.

Due to the obstacles identified for using data from the National Board of Health and Welfare's health data registers to study treatment effects, a number of proposals have been put forth to resolve these in whole or in part:

- To investigate the process of data collection and processing, with an overall goal to more fully utilise the potential in the National Board of Health and Welfare's register information to generate a greater benefit for the patient.
- To overhaul the processes for collecting and making the National Board of Health and Welfare's register data available so that (1) the time between data collection and data publication is reduced, (2) the time between the receipt of an application for data extraction and data access is shortened, and (3) the reporting of certain key variables is improved.

Other experiences: When data were to be extracted from the National Board of Health and Welfare's registers in the beginning of 2020, data for 2018 were still not available in the Swedish Cancer Register. In order to be able to use these data in the evaluation, the pilot awaited the addition of this data to the register. The delayed reporting of data has a negative effect on the possibility to perform follow-up.

The interim report is available in its entirety here

2.6 Pilot study 6:

Purpose: Follow-up of pharmaceuticals used in the treatment of prostate cancer with a qualitative feasibility study and data from Sweden's national health data registers and the Population Register. The purpose of the pilot study is to perform follow-up of the utilisation and effect of the pharmaceuticals Xtandi (enzalutamide) or Zytiga (abiraterone acetate). Both Xtandi and Zytiga are used in the treatment of prostate cancer. No direct comparative studies have been done for these two products, which makes it difficult to compare the treatment effect between the pharmaceuticals. The effect may also differ between different patient groups. Furthermore, the pilot sets out to investigate the conditions for being able to identify patient populations for which the effect between the pharmaceuticals can be compared and to create a study design for in-depth analyses.

Data sources: Focus group interviews with prescribers, population registers from Statistics Sweden and the National Board of Health and Welfare's health data registers: The Prescribed Pharmaceutical Register, the Patient Register, the Swedish Cancer Register and the Cause of Death Register.

Implemented by: Uppsala University

Method: In order to gain an understanding of what influences a prescriber to choose one treatment over the other, a number of in-depth interviews were conducted with the treating physician and data describing the characteristics of the patients were analysed. Based on this, patient groups treated with each pharmaceutical have been identified. A dataset that captures factors that influence the choice between two seemingly comparable pharmaceuticals has been developed. The combination of in-depth interviews and machine learning methodology is then used to create a framework to identify the most important confounders that can be

used to adjust the groups so the two treatments can be compared. An evaluation of how confounders will be handled was done on a dataset created from data from the National Board of Health and Welfare's health data registers and from Statistics Sweden. The primary outcome variable, survival, has not been used in the dataset in order to ensure this does not affect the structure of the design. Secondary outcome measures are inpatient care for severe pain or skeletal-related events and duration of treatment.

Results: The pilot demonstrates that it is possible to create datasets in the health data registers to allow for the side-by-side comparison of two treatments. The combination of in-depth interviews and data analysis revealed, among other things, that prescribers tend to prefer Zytiga for patients with fatigue and poor general condition, while patients with osteoporosis, diabetes and heart disease tend to be prescribed Xtandi.
When developing the study design, it was noted that there is a relatively large regional difference in the proportion of patients treated with Xtandi and Zytiga, respectively. This indicates that there is a good opportunity to identify matched individuals who have similar characteristics but different treatments, which is a prerequisite for being able to compare the two pharmaceuticals. The next step is to link the dataset that has been developed with quality registers that contain data to measure treatment effects and compare this between the two pharmaceuticals. This type of study design, which is used in the pilot study, is extremely time consuming, and the project has now continued for three years.

Other experiences: If the patient population that receives a treatment changes over time, there is a risk that the results of studies on treatment effect will not be reliable. The analysis methods may therefore need to account for the fact that the patient population can change over time.

The interim report is available in its entirety here

2.7 Pilot study 7:

Purpose: Follow-up of diabetes pharmaceuticals using data from quality registers. This pilot study is a continuation of a previous pilot study that was carried out under the government assignment *Follow-up of pharmaceutical utilisation and treatment effects in clinical practice* (reg. no. 03381/2018). The study is intended to investigate how register data can be used to study generalisability of results from clinical studies in clinical practice. Generalisability is examined by comparing patient outcomes in clinical use for patients who meet the formal criteria in the clinical studies with the outcomes in patients who do not meet these criteria.

Data sources: The study uses data from the National Diabetes Register (NDR), the Prescribed Pharmaceuticals Register, the Patient Register, the Cause of Death Register and Statistics Sweden's longitudinal integration database for health insurance and labour market studies (LISA). Data from these registers have been

synchronised at the National Board of Health and Welfare and subsequently analysed at the Centre of Registers Västra Götaland.

Implemented by: The National Diabetes Register (NDR)/Centre of Registers Västra Götaland

Method: Two studies based on register data were conducted, where the glucose-lowering effect of the pharmaceuticals dapagliflozin (Forxiga) and liraglutide (Victoza), respectively, was compared with the effect of sulphonylureas (SUs). In all parts of the population, primary efficacy variables are changes in HbA1c, body weight, systolic blood pressure and eGFR after 6 months of treatment.

The analysis compares the effect in the portion of the population that meets the inclusion criteria for clinical trials (and could theoretically be included in the clinical trial) with the effect in the patients who do not meet these inclusion criteria. As the population that meets the inclusion criteria will obviously differ from the population that does not meet the criteria, methods that can account for this must be used. This is done in two different ways. First, data are evaluated using a method designed to deal with confounders that can affect the clinical outcome using propensity scores (Prezzlers and Kaizers method), and secondly, a method based on flexible prediction models using machine learning and causal inference (Causal Forests) is used. The latter method has the advantage that it is possible to estimate each individual's causal effect with statistical uncertainty, which makes it possible to evaluate clinical effects for a large number of subgroups. Both methods can be used to evaluate whether the effect on clinical outcome is different for patients who met the criteria for inclusion in the trial than for those who could not participate in the trial.

Results: In a registry study where liraglutide was compared to SU, a total of 18,587 patients in the register population were identified. Of these, 2,971 were treated with liraglutide and 15,616 were treated with SU. In the study population, 5,119 (27.5%) met the inclusion criteria for the clinical study (NN2211-1575).

In a registry study where liraglutide was compared to SU, a total of 10,226 patients were identified in the registry population. Of these, 1,051 were treated with dapagliflozin and 9,175 were treated with SU. In the study population, 2,672 (26.1%) met the inclusion criteria for the clinical study (D1690C00004).

Overall, patients treated with liraglutide or dapagliflozin are slightly younger and have a slightly shorter diabetes duration than patients treated with SU. On average, these patients are also slightly higher in weight and have higher HbA1c at the start of treatment.

Both methods used for evaluation indicate that patients who meet the inclusion criteria for the respective study have an effect that is comparable to those patients who do not meet the criteria. Both liraglutide and dapagliflozin perform better than SU after 6 months of treatment. This applies to HbA1c and body weight as well as blood pressure and kidney function. The causal forests method also has the result

that patients with a very high value of HbA1c before the start of treatment show smaller changes in HbA1c than other patients. This is observed for patients treated with liraglutide and those treated with dapagliflozin but given that the number of patients with very high HbA1c before starting treatment is low, the results should be interpreted with caution. Another interesting observation is that there appears to be a better effect on HbA1c in women treated with liraglutide in comparison to men.

Other experience: The primary purpose of the pilot study was to determine whether it is possible to use registry data to evaluate the treatment effect and investigate the generalisability of results from clinical trials in practice. The use of data from the National Diabetes Register (NDR) allows for good coverage of relevant variables in order to perform follow-up of the treatment effect of diabetes pharmaceuticals. Although the registry studies that were performed show similar trends in results and a certain degree of generalisability between clinical trials and everyday utilisation, there are a number of factors that limit the possibility to draw conclusions about generalisability. Further studies are needed that look at other patient groups and treatment methods in order to be able to draw more generalisable conclusions. However, it can be stated that it is possible to evaluate how a treatment differs between individuals, for example, in a population that does not meet the eligibility criteria for a clinical study compared with those who do meet the criteria. As TLV's decisions frequently contain subsidy limits for new pharmaceuticals, it is significant to note that it is possible to evaluate the clinical effect in subpopulations. Often, there is a lack of information about the relative effect for subpopulations, which makes it difficult to identify which patients had the greatest benefit. The effect and benefit of a treatment are often assumed to be greater for patients with a more severe degree of illness than for those with a milder illness. The results of this study suggest that the effect for patients with very high HbA1c values at the start of treatment is slightly less than for patients that start with lower HbA1c values. However, since these results are based on a small number of patients, further analysis is needed to evaluate the observed effect.

The methodology used in the pilot is also of interest for use in the comparative evaluation of different therapies that have not been studied in clinical trials. The continuation of the project could, for example, be a comparative evaluation of liraglutide compared to dapagliflozin.

The interim report is available in its entirety here

3 Results from the pilot studies

Through the pilot studies described in the previous section, TLV has investigated different dimensions of data access and analysis methods to answer the questions: 1) how is the pharmaceutical utilised? and 2) what effect does the pharmaceutical have on health in clinical practice? according to the general schematic model in Section 1.2.1. The model describes questions that may need to be answered with data. One objective of the pilots has been to illustrate areas where access to structured national data needs to be improved in order to answer the question how are the pharmaceuticals utilised. An additional objective has been to apply analytical methods when relevant data are available to estimate the causal relationship between pharmaceutical utilisation and health effects in clinical practice. Figure 6 below shows which main question and what type of variables the respective pilot study addresses according to the schematic overview model.

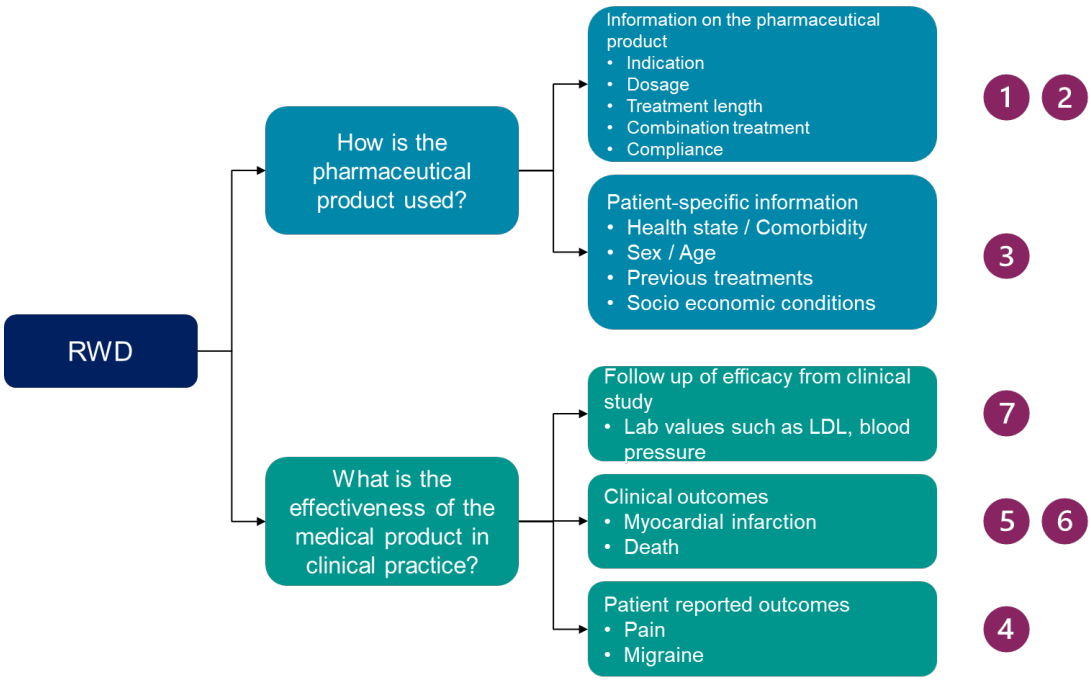

Figure 6. Schematic model of the main questions TLV strives to answer with RWD and examples of variables that may be needed to answer questions about pharmaceutical utilisation and treatment effects in clinical practice. The numbers given in the figure represent the pilot studies and indicate which main question and what type of variables are addressed in each respective pilot study.

3.1 Data is available but is not always available in national government registers

TLV's work in these pilot studies, as well as the agency's experience from previous work, shows that hea21alth data is available, though it is found in a variety of fragmented systems. A portion of the data is available in health data registers. TLV needs continuous access to comprehensive data with good timeliness in order to be

able to perform follow-up of pharmaceutical utilisation and what effect they have in clinical practice. The national government registers, such as the Patient Register and the Prescribed Pharmaceutical Register maintained by the National Board of Health and Welfare, meet these criteria and are also the main data source for TLV.

Even though a great deal of data are already available today, an overall conclusion of the pilot studies is that the methodological approaches that can be applied to evaluate treatment effects in clinical practice may not be able to be used if there are gaps in the underlying data. This is because missing data can lead to unreliable results, regardless of the analysis method. Pilot study 5 examines the usability of four of the National Board of Health and Welfare's health data registers (the Prescribed Pharmaceutical register, Patient Register, Swedish Cancer Register and Cause of Death Register) for follow-up of the clinical effect of two cancer pharmaceuticals. The study shows that several variables that are central for the analysis are characterised by missing data. The missing data are not only significant for information about hospital pharmaceuticals but also for other interventions in specialist care. Diagnostic codes are not always recorded with an adequate level of detail and quality, something that is relevant and necessary when performing follow-up. There is a significant amount of missing data in the registers, which significantly reduces their usability in the follow-up of treatment effects in clinical practice in a more systematic and comprehensive manner. It is also noted that the Prescribed Pharmaceutical register and the Patient Register are updated monthly, which improves conditions for using these for follow-up. In practice, registers that are only updated annually have too long a lag time to be used by TLV in its ongoing follow-up.

As previously mentioned, there is currently no possibility to perform national follow-up of hospital pharmaceuticals on the individual level. The Patient Register can receive data on hospital pharmaceuticals, but the reporting rate is currently so lacking that the data cannot be used for analysis purposes. Within the framework of Pilot Study 1, Region Värmland has automated the reporting of data on hospital pharmaceuticals from the region's data warehouse to the Patient Register. Data reporting takes place monthly and includes information on hospital pharmaceuticals (ATC code level) that are administered in inpatient care or by physicians in specialised outpatient care. The pilot study shows that it is possible to automate data reporting for hospital pharmaceuticals from the region's data warehouse to the Patient Register. If more regions set up equivalent levels of automation, the potential to perform national follow-up of hospital pharmaceuticals on an individual basis should be improved considerably.

The pilot also demonstrates that, in the same way, Region Värmland can generate and automate the transfer of data on hospital pharmaceuticals administered by providers in occupational categories other than physician in specialised outpatient care. However, the Patient Register does not currently include such information.

The pilot studies described above show that there is a need and potential to improve the content of the National Board of Health and Welfare's existing health data registers. The availability of comprehensive national government registers is a prerequisite for performing ongoing and comprehensive follow-up of

pharmaceutical utilisation and treatment effects. In this respect, various quality registers can sometimes serve as an important supplement to the data contained in government registers. But since quality registers are organised around diseases or indications and are dependent on the patient's consent, these registers do not represent a data source that TLV can systematically use in follow-up. In terms of patient-reported data, this information relies on the patient's consent, which indicates that it could be beneficial to store this data in national quality registers.

Patient-reported data is an alternative to health data that is generated based on the delivery of care. Within the scope of Pilot Study 2, a mobile self-care application was used for patients with cystic fibrosis. Using the app, which is a CE-marked medical device, the patient can enter self-reported data on their pharmaceutical utilisation and decide whether they would like to allow the data to be shared with health care providers and quality registers. This pilot study demonstrates that medical technology, in this case a mobile application, can be used to collect patient-reported data for the benefit of the patient himself/herself and can be shared in a structured format with care providers and transferred to quality registers for research purposes and follow-up.

In addition to the lack of access to data on hospital pharmaceuticals, the national health data registers are completely lacking data on laboratory data or corresponding measured values. These data are important for follow-up as the variables can be used to detect slight changes in health over time. Pilot Study 7 studied the treatment effect of two different diabetes pharmaceuticals using data from the health data registers that were supplemented with, for example, data on the measured value HbA1c from the National Diabetes Register (NDR). The pilot shows that when relevant data are available, there are methodological approaches that can be applied to evaluate treatment effects.

The pilot study also demonstrates that laboratory data or equivalent measured values are a key variable in the analysis of a pharmaceutical's treatment effect. In most disease areas, however, access to relevant laboratory data via quality registries is lacking. If it is possible to find ways for the data from the regions' local health and medical care systems to be extracted and processed more regularly to perform national analyses at the individual level, highly favourable conditions are created for the performance of follow-up.

3.2 The evaluation of pharmaceutical utilisation and the effect on health that is achieved requires the use of a variety of approaches

If we look once again at the general schematic model, it becomes clear that data can be used to answer a variety of questions. The two main questions TLV sets out to answer are how a pharmaceutical product is utilised in clinical practice and what effect it has in clinical practice. In order to answer the question of how pharmaceuticals are utilised, pharmaceutical-specific information relating to data on the individual who uses the pharmaceutical is needed. As mentioned above, it is

currently not possible to perform follow-up of the utilisation of hospital pharmaceuticals at the individual level.

TLV's work with the follow-up of pharmaceutical utilisation in the treatment of haemophilia is an example of an evaluation of a prescription pharmaceutical that is used in clinical practice with an emphasis on pharmaceutical-specific questions. In this pilot, the Prescribed Pharmaceutical Register is used to study dispensation patterns for pharmaceuticals used in the treatment of haemophilia, which have been dispensed by prescription at a pharmacy. The pilot study demonstrates that the Prescribed Pharmaceutical Register can be used for follow-up on whether the utilisation of pharmaceuticals in clinical practice supports the assumptions made in the health economic evaluation. Data from the Prescribed Pharmaceutical Register can therefore support the decision-making process when reassessing subsidy decisions.

Before questions can be answered about *what effect* a pharmaceutical has in clinical practice, basic data is also needed about how the pharmaceutical is utilised. In pilot studies 4 and 6, data from the Patient Register are used to examine the group level, which reveals that there may be differences in health status between individuals who receive early access to a pharmaceutical covered by the pharmaceutical benefits scheme and individuals who later gain access to the same treatment. If these differences in the utilisation of the pharmaceuticals are in fact observed, it may be important to consider these differences when choosing an analysis method to evaluate the pharmaceutical's treatment effect in clinical practice. It must be considered, however, that these differences can lead to incorrect conclusions.

The pilot uses data from the National Diabetes Register (DNR) on extrapolation between clinical trials and treatment effects in clinical practice and demonstrates that there are methods for quantifying effects in clinical practice based on the data available in the various existing registers. It is therefore possible to compare the effect achieved in clinical practice with the effect achieved in a clinical trial. However, it is evident that higher demands are placed on data access and relevant methods for answering such a question than are required for generating descriptive analyses of how pharmaceuticals are utilised. If the study design does not randomise patients to one treatment or the other, it is necessary to be able to check for selection bias to avoid drawing incorrect conclusions. The data and methodology used in the pilot show that this type of methodology is available.

4 Conclusions and proposals for continued work

Good opportunities to perform follow-up are central to the development of value-based pricing and thereby contribute to the appropriate utilisation of pharmaceuticals and good access to medicines across the population, all in accordance with the ethical principles for priorities in healthcare. This contributes to the rapid and equal access to new pharmaceuticals and help to ensure that as many people as possible have access to treatment. Good opportunities for follow-up also create the conditions for TLV to follow-up the agency's decisions in order to ensure that the pharmaceutical utilisation results in a reasonable cost, not only when making subsidy decisions but during the entire life cycle of a pharmaceutical.

TLV's work in the pilot studies and experience from previous work show that there is a great deal of health data currently available that could be used for follow-up of pharmaceutical utilisation and treatment effects in clinical practice. The biggest challenge is that the data are found in a variety of fragmented systems and that there is no coherent structure for follow-up on the national level.

Certain data from the health care system is reported to national health data registers and national quality registers. This data is therefore made available in a structured form and is useful for a number of follow-up purposes. Reporting to health data registers is regulated under the Health Care Data Register Act (1998:543) and associated ordinances (2001:707, 2001:708, 2001:709, 2005:363 and 2008:194). This law regulates what data may be included in the registers and defines the obligations of health and medical care providers to submit data to the health data registers. Due to the existing regulations, the coverage rate is generally high in the health data registers and reporting takes place at a particular frequency. On the other hand, reporting to the national quality registers is voluntary, which means that the coverage rate varies between the different disease-specific quality registers. Quality registers are tailored to various diseases and indications and are thus not comprehensive. They also vary in timeliness, and thus do not represent a systematic, useful data source for TLV's ongoing follow-up efforts. However, quality registers can be useful for a variety of other purposes, including TLV's other needs.

Since TLV needs to perform follow-up of total utilisation of pharmaceuticals irrespective of the disease area, the National Board of Health and Welfare's health data registers constitute the basis for the national follow-up of pharmaceutical utilisation and treatment effects in clinical practice.

The following sections describe TLV's need to access fully developed health data registers. In parallel with this, other data sources (e.g. laboratory data) need to be made available to improve opportunities for follow-up. The section continues by

describing the continued work TLV will need to carry out in order to develop value-based pricing.

4.1 TLV needs constitutional support to handle data from health data registers at the individual level

TLV has a significant need to develop collaborations with several actors, such as regions, academia and private actors, who can take on assignments to develop and evaluate methods for follow-up. The agency's collaboration with other actors would be facilitated further if TLV is given the capacity to handle individual data regarding, for example, diagnoses and dispensation or administration of pharmaceuticals. The current lack of access to this data limits TLV's capacity to perform analyses and develop its internal work methods.

The possibility to process health data at the individual level is a basic precondition for being able to fully develop value-based pricing in order to provide the greatest possible health for the tax money. For this purpose, TLV needs to be able to process data from, for example, national health data registers at the individual level. In order to facilitate a more systematic follow-up process, the conditions for the National Board of Health and Welfare to be able to deliver data to TLV also need to be reviewed.

In order to tap the tremendous potential that lies in the data contained in the national health data registers, TLV thus needs to be granted constitutional support to be able to handle data from the national health data registers at the individual level.

4.2 The health data registers need to be further developed

The health data registers maintained by the National Board of Health and Welfare constitute the foundation for follow-up of pharmaceutical utilisation and treatment effects in clinical practice. Below, the health data registers that are the most significant for pharmaceutical follow-up are described. Proposals are also given for measures that should be prioritised for the Patient Register based on TLV's needs, so that comprehensive follow-up of hospital pharmaceuticals and prescription pharmaceuticals can be performed regardless of where in the care chain pharmaceuticals are administered.

4.2.1 The Patient Register

The Patient Register is updated monthly and contains data on diagnoses at the time care is delivered as well as data on interventions in inpatient care and during doctor visits in specialised outpatient care. The data in the register can be used to describe changes in health over time at the individual level. If these data are linked to pharmaceutical utilisation data, the Patient Register can be used to perform follow-up of pharmaceutical utilisation and treatment effects in clinical practice.

TLV believes that the most fundamental need in the short term is to increase the reporting of data on hospital pharmaceuticals to the Patient Register. Data on hospital pharmaceuticals is submitted with a seven-digit ATC code and is a supplement to the activity code, which indicates that pharmaceuticals have been administered. The reporting of other medical interventions needs to be improved and diagnoses at the time of care need to be indicated with more detail than what is typically done today. Additionally, the Patient Register needs to be expanded to include data on care delivered by occupational groups other than doctors in specialised inpatient care. Otherwise, it will not be possible to follow-up on the utilisation of hospital pharmaceuticals administered during a nurse's visit. This is because the registration of data in the Patient Register is based solely on care delivered by physicians. Pilot Study 1 with Region Värmland demonstrated that, from a technical standpoint, data can be produced via medical record systems. At present, the Patient Register does not include such information. A further limitation is that the Patient Register does not include primary care visits. This means that it is not possible to create a comprehensive overview of the care an individual receives. The transition to more close-to-home care underlines the need to include primary care in the Patient Register or another government register. Information on interventions in primary care is particularly important in order to be able to capture the utilisation and effects of medical devices.

By taking the measures listed below in Table 1, the Patient Register could be developed further and thereby create better conditions for TLV to perform more comprehensive follow-up within the tasks assigned to the agency. Overall, this would mean that the Patient Register would be developed into a comprehensive national source of knowledge on care that is provided in the entire health and medical care system, regardless of occupational category and level of care.

Table 1. Goals and proposed measures to further develop the Patient Register.

	Goal	Measures needed
Over the short term	**1) Increase the coverage rate** for data on hospital medicines in inpatient care or during doctor visits in specialised outpatient care in accordance with current ordinances and regulations.	Actors who carry out activities in the health and medical care system and have a duty to report information should increase their reporting to the Patient Register. The National Board of Health and Welfare, TLV and the regions should work together to increase reporting and look to Region Värmland's work with automation as a model.
	2) Increase the coverage rate for data on interventions and specify the diagnosis at the time of care with more detailed coding in inpatient care or during doctor visits in specialised outpatient care in accordance with current ordinances and regulations.	Increase reporting from actors who perform activities in the health and medical care system and who have a duty to report information to the Patient Register. Actors who have a duty to report should submit data to the Patient Register.
	3) Expand the Patient Register to include data from visits in specialised outpatient care with occupational categories other than physician.	The Government should amend the ordinance for the Patient Register so that the National Board of Health and Welfare can handle information from visits in specialised outpatient care that occur with a provider in an occupational category other than physician. The National Board of Health and Welfare amends the regulations. Actors who have a duty to report should submit data to the Patient Register.
Over the long term	**4) Expand the Patient Register** to include data from visits to primary care with all occupational categories reported.	The Government should amend the ordinance for the Patient Register so that the National Board of Health and Welfare can handle information from all visits to primary care. The National Board of Health and Welfare amends the regulations. Actors who have a duty to report should submit data to the Patient Register.

4.2.2 The Prescribed Pharmaceutical Register

The Prescribed Pharmaceuticals Register is updated monthly and contains detailed information on all pharmaceuticals dispensed by prescription at pharmacies as well as information on medical devices dispensed that are covered under the pharmaceutical benefits scheme, such as ostomy care products.

Once the National Medicines List is in place at the e-health authority, the usability of the Prescribed Pharmaceutical Register is further improved, which will then also include information from the National Medicines List on the reason for prescribing.

An issue that is a priority for TLV is the expansion of the Prescribed Pharmaceutical register to include information on hospital pharmaceuticals and, by extension, the reason for ordering. In parallel with the further development of the Patient Register, this would make it possible to perform comprehensive follow-up of pharmaceutical utilisation with a very high level of detail.

4.2.3 *The Swedish Cancer Register*

The Swedish Cancer Register is updated annually and contains data on the occurrence of tumours. Tumour data is an important variable in the follow-up of pharmaceutical utilisation and treatment effects of cancer pharmaceuticals in clinical practice.

Unlike other health data registers, the Swedish Cancer Register contains information that requires the coding of medical data and a search for missing certificates before the data is sent to the National Board of Health and Welfare. It is therefore inevitable that reporting to the register occurs with a certain lag time.

The usability of the register for TLV's purposes would increase if timeliness is improved.

4.2.4 Cause of Death Register

The Cause of Death Register is updated annually and contains all deaths recorded in the Swedish population along with the cause of death. In observational studies that study treatment effects in clinical practice, information on the cause of death is an important outcome measure.

The usability of the register for TLV's purposes would increase if timeliness is improved.

4.3 The availability of laboratory data needs to be improved

TLV often needs access to laboratory data to follow up on subsidy limits and to evaluate the treatment effect in clinical practice. Laboratory data is available locally in the regions' health care systems, but it is generally not made available in national health data registers.

It may be technically possible to identify laboratory data or other relevant data via the national service platform. However, there may be structural and legal limitations to how the data can be made available for joint processing and analysis across regional borders.

If it is possible to find ways for the data from local health care systems in the region to be extracted and processed more regularly to perform national analyses at the

individual level, highly favourable conditions are created for the performance of follow-up of pharmaceutical utilisation and treatment effects in clinical practice. The possibilities of making laboratory data available need to be investigated further.

4.4 Developed health data registers benefit the health care and life sciences sectors

The development of the Patient Register according to TLV's proposed measures in Table 1 in Section 4.2.1 should lead to more complete health data registers. This would help achieve the vision outlined in the National Pharmaceutical Strategy for *Correct Use of Medicines to the Benefit of Patient and Society*. The focus areas proposed for 2020–2022 concern challenges such as the introduction of new pharmaceuticals, pharmaceutical follow-up and the generation of knowledge and evidence. All these areas will benefit from having more complete health data registers, which provide better opportunities for pharmaceutical follow-up and the generation of knowledge.

Creating more complete health data registers, and thus greater opportunities for follow-up, is completely in line with Sweden's life science strategy, which highlights the need to utilise health care data for research and innovation. Data availability is tremendously important for the sector as well as academia and other agencies. And the ongoing coronavirus pandemic has illustrated the importance of being able to follow-up on both care utilisation and which pharmaceutical treatment is used in real time. To be able to systematically follow-up on all treatments involving pharmaceutical utilisation, regardless of whether the pharmaceutical is prescribed or not, creates completely new opportunities for follow-up of both the clinical effect and potential side effects.

It may also become easier to introduce advanced therapy medicinal products (ATMPs) or costly pharmaceutical combinations if the health data registers are more complete. This is due to improved conditions to be able to design payment models or agreements that reduce the cost for use through reimbursements that are calculated using data from the health data registers.

4.5 TLV's continued work

The agency's experience from the work carried out thus far is that continuous and long-term work is needed to develop access to relevant data and to evaluate methods for follow-up. The ultimate goal is to develop the possibility to use information about pharmaceutical utilisation and treatment effects in clinical practice for subsidy decisions over the entire life cycle of a pharmaceutical. TLV has determined that there is tremendous potential to develop access to data and to make data available. This data is currently found in fragmented systems in the health care sector. In addition to developing access to relevant data, TLV also needs to continue its work in identifying relevant methods for follow-up.

The agency's experience also shows that increased collaboration and communication between different actors and agencies is needed if we are to gain greater knowledge about how pharmaceuticals are utilised and their effects in clinical practice. In order to improve collaboration between agencies, TLV sees that one path forward is to address these issues within the framework of the work with the Council for Knowledge Management, where several agencies collaborate.

TLV is engaged in an ongoing government assignment *Expanded follow-up using the national service platform,* which the agency must report no later than 1 May 2021. Within the scope of the assignment, the agency is investigating, for example, the possibilities to extract data for follow-up of pharmaceuticals and medical devices from the regions' medical record systems. The possibilities to extract data directly from the journal systems are investigated as well as the possibilities to indirectly extract data via other systems, such as the national service platform. The ongoing assignment provides some continuity in TLV's work, as the major questions largely overlap with those addressed in this assignment.

The agency sees that there is a continued need to work to develop access to relevant data and to evaluate methods. In order create continuity and a long-term vision, TLV needs a continued assignment that runs over a couple of years. The assignment should look further into how to increase availability of relevant health care data for pharmaceutical follow-up in health data registers or via alternative methods. The assignment should also investigate methods for follow-up of treatment effects in clinical practice.

Appendices

Pilot study 3:
https://www.tlv.se/download/18.1fc7385174b9d2fac779938/1601389180622/pilotstudie3_battre_uppfoljning_av_antibiotikaanvaandning_vid_cystisk_fibros.pdf

Pilot study 4:
https://www.tlv.se/download/18.1fc7385174b9d2fac779939/1601389180635/Pilotstudie4_att_studera_effekter_av_medicinska_interventioner_i_klinisk_varda.pdf

Pilot study 5:
https://www.tlv.se/download/18.1fc7385174b9d2fac77993a/1601389180647/pilotstudie5_behandling_klinisk_vardag.pdf

Pilot study 6:
https://www.tlv.se/download/18.1fc7385174b9d2fac77993b/1601389180659/pilotstudie6_enzalutamide_mot_abiraterone.pdf

Pilot study 7:
https://www.tlv.se/download/18.1fc7385174b9d2fac77993c/1601389180672/pilotstudie7_statistiska_metoder_for_utvardering_av_heterogenitet_i_kausala_effekter.pdf