Using Routinely Collected Data to Inform Pharmaceutical Policies

Analytical Report for OECD and EU countries

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https://ec.europa.eu/health/policies/costeffective_medicines_en

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Summary

A consensus is emerging on the need to exploit the rich information health systems generate to drive both enhanced outcomes for patients, and better economic performance, including in the pharmaceutical domain. The prices and reimbursement conditions of new medicines are often determined just after market entry, based on evidence of risks and benefits generated in pre-registration clinical trials. However, the use of these medicines in routine clinical practice sometimes leads to the emergence of unanticipated outcomes (rare or delayed adverse effects not detectable in clinical trials; variable clinical results) and very often reveals a gap between efficacy (benefits assessed in clinical trials) and effectiveness (benefits observed in clinical practice). Retrospective observational studies, using appropriate analytical methods, can therefore help in assessing the value of medicines in use in healthcare systems.

This report provides an overview of patient-level data on medicines routinely collected in health systems from administrative sources, e.g. pharmacy records, electronic health records and insurance claims. In total 26 OECD and EU member countries responded to a survey addressing the availability and accessibility of routinely collected data on medicines and their applicability to developing evidence. The report further explores the utility of evidence from clinical practice, looking at experiences and initiatives across the OECD and EU.

Most responding countries collect patient-level data on medicines in routinely, usually from pharmacy records, electronic health records or insurance claims. These databases rarely cover medicines dispensed in hospitals, which is a significant gap.

OECD and EU member countries do not have equivalent capacities to harness routinely collected data in the management of medicines. Technically, many countries are able generate a wide set of information related to patient healthcare consumption, diagnoses, causes of death, either because the information is directly available in databases containing information on medicine consumption, or because the databases can be linked with other databases that do. Countries such as Korea, Israel, Romania, Sweden, and the United States (for sub-populations), report substantial potential in terms of available information. Other countries, for example Austria, Ireland, and the Netherlands are less likely to use routinely collected data to inform pharmaceutical policies and assess the performance of medicines in clinical practice.

Responding countries have varied health systems both in terms of health care coverage (government scheme vs health insurance, single insurer vs multiple insurers) and pharmaceutical management (single vs multiple institutions in charge of regulation/HTA/reimbursement and pricing decision).

- About half the responding countries reported that routine databases were only accessible to government agencies and data custodians. In many cases, health care payers and all public institutions involved in decision-making can access these data.
- Twelve countries reported that, in addition, universities and non-profit research units may access these data; by contrast, this does not seem possible in Italy, Lithuania, Luxembourg, the Netherlands or Romania.

- In a few countries, data are accessible to other stakeholders: for example Commissioning Groups in England, GPs in the Netherlands, the pharmaceutical industry in Australia, and all stakeholders in France, as long as their research is in the public interest and the results are shared with public health authorities.

While routine data are widely collected, they are not systematically used to inform pharmaceutical policies. Responding countries primarily use routinely collected data on medicines to monitor consumption and national level spending (22 countries), providers' compliance with guidelines (18 countries), and prescribing quality and behaviour (15 countries). Fourteen countries use routine data to evaluate the safety of medicines and to inform changes in clinical practice. About half the responding countries also consider routinely collected data on prescribed and dispensed medicines in cost-effectiveness studies and comparative effectiveness evaluations.

Getting a complete picture of how these data are used is a complex endeavour; studies drawing on the data are not all made publicly available. Those studies that are available may be published in different national languages, and not all are indexed in bibliographic databases, and only a fraction of them are published in peer-reviewed journals. According to existing literature reviews, to date about 2 000 peer-reviewed pharmaco-epidemiology studies drawing on the Clinical Practice Research Datalink database in the United Kingdom have been published; about 340 scientific publications from the Swedish Prescription Register and 176 from the French SNDS database.

Assessing the impact of the studies drawn from routinely collected data on pharmaceutical policy development is even more challenging. Evidence generated from observational studies and clinical practice are used to inform HTAs more often than they are used to guide decisions on marketing authorisation by regulatory agencies. Partly, this is due to timing issues, since routine data by definition are only available from the time a technology is diffused. In addition, the traditional evidence hierarchy prevents routinely collected data from being central to decision-making. As a result, these data often play a supporting role in evaluations and assessments. The report highlights a few examples provided by countries or found in the literature.

- Generally, **regulatory agencies use routinely collected data in post-market safety surveillance and for ad-hoc risk-benefit re-assessment**. The report provides a number of examples where regulatory agencies have used evidence derived from routinely collected data to confirm or counter suspected safety concerns. Depending on the results, such evidence has led to market withdrawal, safety notifications and labelling changes, modified indications, or confirmation of the initial terms of marketing authorisation.
- **Institutions in charge of HTA consider evidence derived from routinely collected data to revise their assessments of medicines.** In France, for example, information on misuse led to a downgrading of the assessed therapeutic value of benzodiazepines and a subsequent reduction in the reimbursement rate. In Ireland, evidence derived from routine collected data was used to recommend a specific product for smoking cessation programmes.
- Fourteen responding countries reported that **observational studies based on routinely collected data have sometimes influenced decisions on coverage conditions or prices**, for example in Australia, Estonia, Finland, and France.

- **Evidence from routinely collected data has also driven changes in clinical guidelines**, for example for attention deficit hyperactivity disorder (ADHD) medicines in Australia, and statins in Israel. In the United Kingdom, a study of the safety of pertussis vaccine in pregnant women supported the continuation of the vaccination programme.

Although routinely collected data hold great potential, countries recognise that these data are not used to their full capacity. Lack of resources and analytical capacities are identified as the key barriers to better integrate the use of routinely collected data in pharmaceutical policy development. Many countries also face legislative and regulatory barriers, which limit data sharing and linkages, and prevent further use of these valuable data. However, these barriers are currently being addressed, e.g. through implementation and strengthening of health data governance arrangements, and the more complete implementation of technologies to secure patient privacy.

OECD and EU Member States could certainly advance the use of routinely collected data to support better pharmaceutical policy-making:

- Methods to derive evidence from routinely collected data, especially for assessing effectiveness and comparative effectiveness, need to be further developed and to gain greater legitimacy and recognition from HTA agencies. Deriving evidence from routinely collected data presents certain challenges, such as reporting burden and outcome attribution. In the long run developing such methods provides the surest route to provide confirmatory evidence of a product's value to the health system.
- Countries that lag behind in terms of data infrastructure and governance may benefit from upgrading their capacity to harness the data routinely generated within their health systems, in line with the recommendations of the OECD Council on data governance and with reference to best practices in OECD countries. As “lack of capacity and resources” is the most frequently cited reason for the under-use of routinely collected data, countries might also review the means allocated to these activities, whose impact on patient outcomes and efficiency may be high.
- Cross-border knowledge sharing could be improved if all studies that are relevant, topical, transferable to other contexts, and that present actionable results, were published in peer-reviewed journals and systematically considered by HTA agencies and decision-makers during the life-cycles of the products in question.

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
AIFA	Italian medicines agency
ANSM	French medicines agency
APCD	All-payer claims databases
ARR	Adjusted relative risks
ATC	Anatomical therapeutic chemical classification system
CCAM	Medical and dental procedures, identified by codes of the fee schedule, France
CER	Comparative effectiveness research
CHC	Combined hormonal contraceptives
CNAMTS	French national health insurance fund for salaried employees
CNIL	French national commission on data privacy
CPRD	Clinical practice research datalink
CT	French national transparency commission
DDD	Defined daily doses
DRG	Diagnosis-related groups
DUSC	Drug Utilisation Sub Committee
EBM	Evidence-based medicine
EHDEN	European Health Data and Evidence Network
EHIF	Estonian Health Insurance Fund
EHR	Electronic Health Records
EMA	European Medicines Agency
EMIF	The European Medical Information Project

EU	European Union
EUR	Euros
FDA	The Food and Drug Administration
HAS	French High Authority for Health
HHS	Department of Health and Human Services, United States
HIQA	Health Information and Quality Authority, Ireland
HIRA	Health Insurance Review and Assessment Service, Korea
HPV	Human papillomavirus
HSE	Health Services Executive, Ireland
HSE-PCRS	Health Service Executive - Primary Care Reimbursement Service, Ireland
HTA	Health Technology Assessment
IMA-AIM	InterMutualistich Agenschap–Agence InterMutualiste, Belgium
IMI	Innovative Medicines Initiative
IMS	Intercontinental Marketing Statistics
INDS	National Health Insurance Fund, France
INFARMED	National Authority of Medicines and Health Products
IS	Ischaemic stroke
ISAC	Independent Scientific Advisory Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCE	Belgian Health Care Knowledge Centre
KELA	Social Health Insurance Institutions, Finland
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid lowering therapy
MA	Market Authorisation

MACE	Major adverse cardiac events
MEPS	Medical Expenditure Panel Survey
MI	Myocardial infarction
MMP	Medicines Management Programmes
MPCD	Multi-payer claims database
NBAM	Biological tests performed, identified by codes of fee schedule
NDA	New Drug Application
NHS	National Health Service
NICE	National Institute for Health and Care Excellence, United Kingdom
NOACs	Novel oral anticoagulants
NRT	Nicotine replacement therapy
NVAF	Non-valvular atrial fibrillation
OECD	Organisation for Economic Co-operation and Development
OMOP	Observational Medical Outcomes Partnership
OTC	Over-the-counter medicines
PBAC	Pharmaceutical Benefits Advisory Committee, Australia
PBS	Pharmaceutical Benefit s Scheme, Australia
PCORI	Patient-Centered Outcomes Research Institute
PE	Pulmonary embolism
PECUNIA	ProgrammE in Costing, resource use measurement and outcome valuation for Use in multi-sectoral National and International health economic evaluAtions
PMR	Post-market Reviews
PMSI	Program of Medicalisation of Information Systems, France

PR	Pharmacy records
PRAC	Pharmacovigilance Risk Assessment Committee
RC	Reimbursement claims and billing information
RCT	Randomised Controlled Trials
RR	Rate ratio
RR	Relative risks
RRR	Ratio of the rate ratios
RWD	Real world data
RWE	Real world evidence
SACT	Public Health England's Systemic Anti-Cancer Therapy
SNDS	National system of health data, France
SNIIR-AM	The Statutory Health Insurance interscheme information database, France
SPRD	Swedish Prescribed Drug Register
TGA	Therapeutic Goods Administration, Australia
THIN	The Health Improvement Network, United Kingdom
TT	Testosterone treatment
VA	Department of Veterans Affairs, United States
ZIN	Dutch Health Care Institute

Introduction

1. In health systems, big amounts of data are routinely collected from clinical practice. These data can potentially be used to assess and monitor the effectiveness and safety, as well as the costs of medical technologies. Evidence derived from routinely collected data could provide valuable insights for OECD and EU member states facing several challenges: fiscal pressure on health budgets; rising expectations of access to safe, evidence-based care; the increasing number of treatments targeting small population groups; the growing availability of rich datasets and the technology with which to exploit them. Many policy experts agree that conventional randomised controlled trials (RCTs) are no longer sufficient for informed decision-making for systems that want to move from being mere payers to more prudent purchasers of health products and services. However, the use of evidence from clinical practice still varies widely across the EU and the OECD. Some countries are using evidence from clinical practice to inform coverage and payment/pricing decisions, while others are harnessing routinely collected data to improve care.

2. The supply of routinely collected data is reaching a crescendo in many countries with the collection of electronic patient-level data. A sufficient volume of accurate data coupled with modern analytical techniques can complement existing sources of evidence regarding the safety, effectiveness and cost-effectiveness of health care interventions and technologies. Evidence from clinical practice, particularly if derived from large routine datasets, can complement information derived from clinical trials, since not every comparative research question of importance is appropriate to answer in a clinical trial setting. This can not only improve care quality, but can also enhance the utility of health technology assessment (HTA), and inform regulatory and reimbursement decisions to achieve greater value and allocative efficiency (OECD, 2017[1]).

3. While RCTs remain the 'gold standard' for collecting the data required for marketing authorisation, the importance of evidence from clinical practice is increasing in terms of positioning a drug for pricing and reimbursement, providing validated long-term insights for health care providers, showing value for money for payers, and enabling best care for patients. Decision makers involved with coverage and payment policies are increasingly seeking information on real world outcomes on which to base their decisions. Many of them are developing policies that integrate evidence from different sources. These policies recognise the importance of evidence that goes beyond the RCT evidence collected during clinical development, required by regulatory authorities for marketing approval.

4. This paper is informed by previously conducted OECD studies on health data governance, and a survey distributed in 2018 to all OECD and EU Member States aiming to map countries' collection, uptake and utilisation of routinely collected data in pharmaceutical policy-making. Section 1 of this paper defines the scope of the study as well as distinctions between key terms often used interchangeably in the realm of evidence from clinical practice. Section 2 explores the type of evidence from clinical practice that can be derived from routinely collected data. Section 3 probes the **availability**, **accessibility** and **applicability** of routinely collected data in OECD and EU Member States. This sets the stage for Section 4, which through a set of country-specific case studies, demonstrates the **actionability** of evidence derived from routinely collected data to inform marketing authorisation, health technology assessment, pricing and reimbursement decision-making, and guide clinical practice. Finally, the conclusion provides recommendations for OECD and EU Member States to facilitate the further exploitation of the potential of routinely collected data.

1. Defining key terms and scope of the study

5. This report focuses on routinely collected data on prescribed and dispensed medicines, i.e. data collected systematically when patients interact with health care providers, for instance through reimbursement claims, electronic health records, pharmacy records, and hospital discharge data. The emphasis is on administrative, routinely collected data, excluding other data sources in a wider range of *real world* data (e.g. data collected in pragmatic clinical trials, genomic data, biobanks, or social media). Routinely collected data is thus only *a subset* of Real World Data (RWD). Real world evidence (RWE) is the evidence generated by answering research questions using real world data.

This section discusses and defines the key terms and the scope of the study. Section 1.1 below discusses prior definitions and RWD and RWE in the literature and section 1.2 defines routinely collected data for the purposes of this report.

1.1. Defining real world data (RWD) and real world evidence (RWE)

6. There are ambiguities surrounding the definition, scope and sources of the terms "real world evidence" and "real world data". While RWD and RWE are often used interchangeably, they really are quite different concepts. RWD is a term used to describe health care related data that are collected outside the context of randomised clinical trials (RCTs), whereas real world evidence is defined as the *insight* or *knowledge* derived from the analysis of real world data, conducted to respond to a specific research question[1]. The notion of "data" conjures the idea of simple factual information, whereas "evidence" connotes the organisation of information to inform a conclusion or judgment. Evidence is generated according to a research plan and interpreted accordingly, whereas data are just one component of the research plan. Evidence is shaped, whereas data are simply raw material and are uninformative in the absence of analysis and interpretation.

7. Nearly a decade ago an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) taskforce defined RWD as "data used for decision-making that are not collected in conventional randomized controlled trials." The ISPOR taskforce focused on the use of RWD for coverage and pricing and concluded that RWD are essential for sound decision making. Nevertheless, it also highlighted that it is critical that policy makers recognise the benefits, limitations, and methodological challenges in using RWD, as well as the need to consider carefully the costs and benefits of different forms of data collection in different situations (Garrison et al., 2007[2]).

8. The "Get Real" initiative, a research consortium of the Innovative Medicines Initiative (IMI), co-funded by the European Commission and the pharmaceutical industry, defines RWE as "the evidence derived from the analysis and/or synthesis of real-world data (RWD)" (Makady and Goettsch, 2013[3]). RWD are in turn defined as "data regarding the effects of health interventions […] that are not collected in the context of conventional randomised controlled trials […] [but] prospectively and retrospectively from observations

[1] Different versions of this definition exist. Under the US' Food and Drug Administration's RWE program, evidence derived from various hybrid or pragmatic trial designs and observational studies could generate RWE (FDA, 2018[39]).

in routine clinical practice […] from many sources including patient registries, electronic medical records, and observational studies" (ibid.).

1.2. Routinely collected data is one type of "real world data"

9. This report focuses on routinely collected data on prescribed and dispensed medicines. Routinely collected data are only a subset of Real World Data (RWD). One way to categorise routinely collected data is by type of data source. While there is no international consensus on what constitutes a valid routine data source, the value of this classification is that it identifies tangible sources of information, such as:

- Administrative datasets
- Electronic health records
- Patient registries
- Regularly conducted health surveys

10. Routinely collected data refer to data that are generated in administrative processes or clinical care and whose primary purpose is to support these processes and care. Examples include hospital discharge data, prescription dispensing, emergency department attendances, insurance claims and death certificates. These datasets lend themselves to secondary and retrospective analyses, longitudinal or cross-sectional, of exposures and clinical and economic outcomes at the patient-, patient group-, or population-levels. Issues can arise in the analyses of these datasets as they are not initially generated for research purposes.

11. Administrative data or 'insurance claims' make up a broad category of data sources and usually refer to information held by health care payers and derived from reimbursement claims by patients or billing information from providers.

12. Electronic Health Record (EHR) systems hold a specific type of routinely collected data on patient medical histories. These data are generally maintained by the provider over time, and may include patient characteristics and all of the clinical data relevant to a patient's care received from a particular provider, including demographics, progress notes, problems, medications, vital signs and clinical examination notes, past medical history, immunisations, laboratory data and radiology reports. The potential of EHR is a priori higher than that of claims data (since they include diagnoses and tests results). The inclusion of patient-reported outcome measures and patient experiences could increase the potential utility of these data.

13. Data in registries can be collected for various purposes and are, for the purposes of this report, only considered within the scope of routinely collected data if the registry in question is perennial and its purpose is not limited to a specific post-market study. Data in registries are generally collected prospectively from patients who have a particular disease and/or are receiving a particular treatment or intervention. Data collected in general disease-based registries can be used for retrospective observational studies. For example, cancer registries may be used to assess clinical and treatment characteristics over time. In other cases, however, registries are established for a specific research purpose, for example to collect post-marketing safety data, either in response to specific safety concerns or to fulfil regulatory obligations established as a condition of marketing authorisation. In the latter case, data in the registry are primarily collected for a research purpose and are not considered to be *routinely collected*.

14. Health surveys are designed to collect descriptions of health status and well-being, health care utilisation, treatment patterns, and health care expenditures from patients, providers, carers or individuals in the general population. When they are conducted periodically to serve a wide range of purposes in research, policymaking and health system governance, they are considered routinely collected data for the purposes of this report.

15. Evidence derived from the sources described above cannot replace the safety and efficacy data generated by RCTs. Rather, they can complement RCT data by allowing, for example, actual effectiveness versus expected efficacy and safety to be evaluated in the context of a routine clinical setting. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under routine conditions. Although efficacy research increases the likelihood of observing the effect of an intervention if such an effect exists, effectiveness research accounts for external patient, provider, and system-level factors that may modify an intervention's effect (see Singal, Higgins and Waljee (2014[4]) for a discussion of efficacy and effectiveness).

16. Routinely collected data may include health-related information, including diagnoses and health outcomes, and/or resource use and financial outcomes. Health and financial outcomes refer to:

- Clinical outcomes include measures of morbidity and mortality (e.g., survival, myocardial infarction, stroke)
- Surrogate endpoints include e.g., systolic blood pressure, LDL-cholesterol, HbA1c. Much of the data collected in phase III pre-registration trials involve surrogate endpoints. By contrast, real world data can provide a data on longer-term clinical outcomes.
- Patient-reported outcome is the term used to encompass any report coming directly from patients about a health condition and its treatment, including symptoms, functional status, quality of life, treatment satisfaction, preference and adherence.
- Economic/financial outcomes include estimates of medical and non-medical resource utilisation and their associated costs.

17. Traditional hierarchies of evidence rank studies according to the strength of the research design in achieving internal validity. Historically, the use of evidence hierarchies has been central to evidence-based medicine (EBM) and EBM proponents stress the need for clinical researchers to document all study protocols, utilise appropriate analytical techniques, and strive for internal validity. Studies are considered externally valid when findings are generalisable beyond clinical trial setting. Typically, data from (meta-analyses of) RCTs sit atop the hierarchy followed by data from non-randomised intervention studies, followed by epidemiological studies and so forth (Masic, Miokovic and Muhamedagic, 2008[5]). Evidence hierarchies provide a useful ranking based on the rigour of the research design; however, they do not provide a complete and nuanced understanding of evidence from clinical practice.

18. Data collected through health surveys can potentially be used to generate evidence from clinical practice, as these surveys often consider the use of medical products, procedures and health status. However, a set of requirements must be satisfied for health survey data to be included in performance assessments. First, collecting data on the performance of a medicine or health product requires that the surveyed population can be followed up over time. Second, the information on the use of medical services and medical products needs to be complete and accurate. Third, the surveyed sample needs to be sufficiently large and representative of the overall population.

2. Deriving evidence from routinely collected data presents certain challenges

19. While RCTs provide a "gold standard" in the sense that they provide evidence of high internal validity of product efficacy under carefully controlled conditions, RCTs are carried out using selected populations under ideal conditions, which can limit their utility. Despite ranking highest in the evidence hierarchy, evidence derived from RCTs may still be influenced by systematic errors, or bias (Rothman, 2014[6]). Nevertheless, RCTs have many advantages: pre-specified and well-defined endpoints (in many cases) and randomisation of study subjects to intervention and control groups all work to provide unbiased measures of impact in the trial population. However, these characteristics that result in strong internal validity also limit the external validity of RCTs, and their generalisability about which interventions work best when implemented in different settings and populations.

20. The benefit of 'real world' studies in comparison to RCTs is that the results can have greater external validity and be more generalisable. This makes such studies more useful for:

- Estimating the effectiveness (rather than the efficacy) of an intervention in a variety of routine practice settings;
- Comparing multiple alternative interventions (e.g. older vs. newer drugs) or clinical strategies to inform optimal therapy choices beyond placebo comparators;
- Examining clinical outcomes in a diverse study population that reflects the range and distribution of patients encountered in routine clinical practice.

21. The current popularity of routinely collected data stems partly from the availability of unprecedented volumes of data and increasing computational capability and infrastructure to generate and analyse information on the use, benefits and risks of medicines. However, not all data generate useful information and not all information constitutes evidence, so it is important to examine what sort of evidence can be derived from routinely collected data.

22. First, there are differences in the potential of routinely collected data according to their collection and storage methods. Insurance claims data are the most commonly available source in many countries but their purpose is to facilitate payments to patients or providers, thus their scope is often limited to spending and use. Coding schemas often vary across different settings of care, such as between physician records and hospital discharge data. Linking such sources to extract the information of interest can be technically (and legally) challenging. The uptake of EHR technology is permitting routine datasets available for research.

23. The utility of routinely collected data in monitoring product safety is already well-established but is still being discussed with respect to measuring effectiveness. A number of difficulties arise when using routinely collected data to estimate the effectiveness of an intervention. For example, serious adverse events (i.e. ones that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation) that inform assessments of safety are relatively easy to capture and detect in some routine data sets. By contrast, health outcomes that are needed to assess effectiveness (for example the change in a surrogate endpoint, such as systolic blood pressure) and to control for confounding are not always captured in routine data sets and

notably not in insurance claims data. In addition, health outcomes may be recorded less accurately in routinely collected data, so data may be of lower quality than that collected in controlled research settings. There is no "random allocation of treatment" in retrospective analyses of routinely collected data. Intervention groups can therefore have fundamentally different characteristics than control groups, which makes it methodologically difficult to make causal inference and isolate the treatment effect from confounders. Effectiveness can also depend on a number of factors that are not related to the effect of a treatment *per se*, including appropriate use, patient comorbidities and treatment adherence. Claims data, for example, provide information on the prescription and purchase of medicines, but rarely include information from which the appropriateness of the prescription or the patient's adherence to treatment may be inferred. These questions must be addressed before the use of routinely collected data can be expanded.

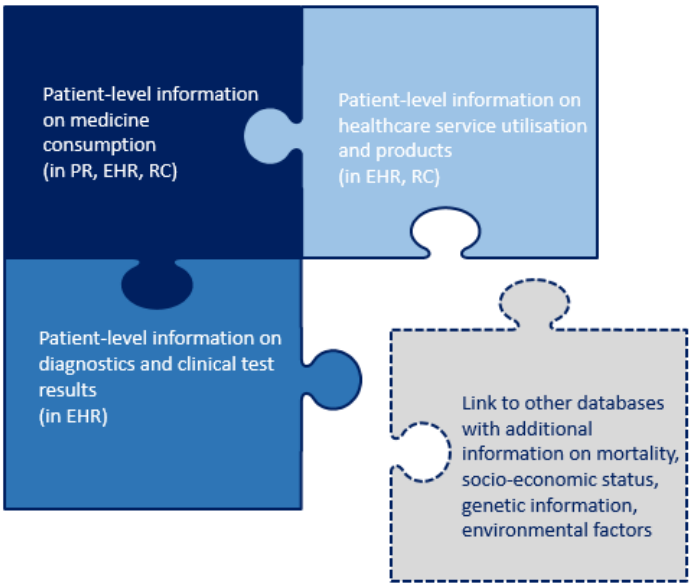
24. New types of targeted drugs and technologies, the rising cost of pharmaceutical R&D, and the emergence of more flexible regulatory options have spurred interest in using routinely collected data more broadly. The move towards precision medicine has led some to argue for a shift away from RCTs, as a result of a paucity of patients with the same disease profile making patient recruitment for RCTs difficult (see Eichler et al. (2018[7]).

3. Countries are unevenly prepared to harness the potential of routinely collected data

25. The use of routinely collected health care data to generate evidence requires first, that appropriate high-quality data are collected, and second, that they are made available to those who conduct research or make decisions. This section summarises the preparedness of countries to use routinely collected data in pharmaceutical policy-making. It is based mainly on results of a 2018 OECD Health Division survey that focused on routinely collected data on prescribed and dispensed medicines.

26. Routinely collected data on prescribed and dispensed medicines reflect a key component of patients' interactions with the healthcare system. Data on these interactions can be extracted from pharmacy records, personal health records, reimbursement claims and billing information. The richest data sources extend beyond prescribing and dispensing to information on health services and outcomes. These datasets either capture this information or can be linked with other health and healthcare datasets containing broader information (See Figure 3.1).

Figure 3.1. Main sources of routinely collected data on prescribed and dispensed medicines



Notes: PR: Pharmacy records, EHR: Electronic Health Record, RC: Reimbursement claims and billing information
Source: Authors.

27. Use of health and health care data for research and policy-making entails both risks and benefits. Health data are personal because they can identify individuals and sensitive because they reveal information about the health status of individuals and the health care they receive. Data generated in health care may arise from confidential relationships between health care professionals and patients. Use of such data for purposes other than for the care of the person to whom they pertain is referred to as secondary use. Secondary use of health care data requires researchers and other third parties to have access to information

to which they would not otherwise be privy because they are not party to this privileged relationship, or because disclosure of the data to researchers and other third parties is restricted under applicable law or policy.

28. The availability, governance and use of routinely collected data have previously been a focus of OECD work, with several studies published since 2011. The 2013/2014 Survey on data infrastructure and governance and the 2016 Survey on EHR design and secondary use have also both been used to inform this section. Complete results were published within comprehensive reviews of health data availability, governance and use in OECD member states, covering, among other aspects, the legislative framework, data collection and retention, data access, project approval and data security (OECD, 2015[8]) (Oderkirk, 2017[9]). In 2018, the OECD conducted a new survey with the objective of mapping current practices and use of routinely collected data on prescribed and dispensed medicines in OECD and EU Member countries.

3.1. Availability: More than half the responding countries collect data on prescribed or dispensed medicines, but linkage with other health or health care datasets is less common

29. The 2018 OECD survey of routinely collected data on prescribed and dispensed medicines revealed that countries are at different stages of data infrastructure and development. Some countries initiated data collections and established prescription databases in the 1990s, while others are only about to start. The 2018 survey also assessed the extent to which the routine databases on medicine usage capture patient-level information beyond prescribing and dispensing data, or may be linked to other databases that do. Twenty-six countries responded to this 2018 Survey.

3.1.1. At least 25 countries collect routinely data on prescribed and dispensed medicines

30. The 2018 OECD survey identified at least 25 OECD and EU Member States that collect routine data on prescribed and dispensed medicines (Table 3.1. Databases with routinely collected data on prescribed or dispensed medicines in OECD and EU Member States). The majority of responding countries collect data nationally and make them available in a single, national-level database: for example, the reimbursement claims databases in Australia, Czech Republic and France and the national prescription databases in Estonia, Finland, Norway and Sweden. In Portugal, routine data are aggregated nationally, but data on reimbursed and prescribed medicines are kept in two separate databases. While reimbursement claims are obtained from pharmacy invoices to the NHS and kept in the reimbursement (CCF) database, data on prescribed medicines are kept in the prescription database (PEM) built from EHRs, and updated by physicians. In countries where data are collected at the regional or health insurance scheme level, such as Belgium, Italy, Luxembourg and Romania, the data are aggregated and made available in national databases.

31. The Nordic countries have all established national, population-wide prescription registries. Finland established the first nationwide registry in 1993, followed by Denmark in 1994, and Norway, Sweden and Iceland established their respective registries in the mid-2000s. The prescription registries include information on electronically submitted prescriptions dispensed to patients by pharmacies, and are updated on a monthly basis. Sharing a similar data infrastructure and content, the registries facilitate record linkage and

collaboration between the countries, and are often used in pharmaco-epidemiological research as well as to inform HTA and decision-making processes.

32. Israel and Malta collect routine data on prescribed and dispensed medicines at the level of the pharmacy and health insurer, and keep these data in separate databases. In Malta, the data infrastructure does not enable national-level data aggregation, as the data are in the custody of each dispensing pharmacy. In Israel, healthcare services and medicines are covered through one of the four health insurance funds (Clalit, Maccabi, Meuhedet and Leumit) that provide mandatory health insurance. Each of the four health insurance funds collects patient-level routine data on their respective insured populations in separate databases. Although the routine data are not aggregated to the national level, the databases within each health insurance fund include rich data often used in research.

33. In the United States, the fragmentation of the health system results in a wide range of different data collection and aggregation practices. Data collections respond to specific data needs. While the household Medical Expenditure Panel Survey (MEPS) includes data on the use of healthcare services and medicines and may in part inform monitoring of medicine consumption and national expenditure, it is unlikely to support research on medicines safety or performance. Some data collections are carried out at the State-level with databases remaining at the State-level. Private companies, like IQVIA, initiate routine data collections and in some cases aggregate these data nationally.

34. Some federal agencies collect routine data in the United States. The federal Government aggregates data on specific sub-populations, such as the elderly population covered by Medicare. The Food and Drug Administration (FDA) Sentinel Initiative uses a distributed data approach that allows the FDA to monitor the safety of regulated medical products, while safeguarding patient privacy. Patient details are not collated centrally. Instead, by using a common data model, standardised input files are generated locally by each of the 18 data partners, and sent in de-identified and encrypted format to a central database for evaluation and analysis. The Sentinel Distributed Database comprises 292.5 million cumulative patient identifiers between 2000 and 2017, and includes data on 14.4 billion instances of pharmacy dispensing, 13.3 billion unique medical encounters and 45.6 million patients with at least one laboratory test result.[2]

35. The Patient-Centered Outcomes Research Institute (PCORI), created to promote development and adoption of comparative effectiveness research (CER), also funds a US-wide initiative to integrate administrative data sources and make them accessible for comparative effectiveness research (PCORI[61]). Among its activities, PCORI has developed a multi-payer claims database (MPCD) to become a repository of Medicare data and private health insurance claims, thereby enabling researchers to implement observational studies. This project has been underway by the U.S. Department of Health and Human Services' (HHS) Office of the Assistant Secretary for Planning and Evaluation (ASPE) since 2009, and ASPE has been developing strategies for creating, operating, and maintaining the MPCD for CER and other uses. The MPCD is a private/public partnership with the goal of consolidating access to longitudinal data on health services to help facilitate CER. Over time, the goal is to extend it beyond claims data with additional clinical detail from other sources, such as EHRs. In addition, at least 19 states have enacted all-payer claims databases (APCDs), requiring insurance carriers to contribute their insurance claim

[2] https://www.sentinelinitiative.org/sentinel/data/snapshot-database-statistics , accessed 23/11/18

logs into a single data warehouse for the benefit of researchers and consumers (APCD Council, 2018[10]).

Table 3.1. Databases with routinely collected data on prescribed or dispensed medicines in OECD and EU Member States

Country	Name of prescribing/ dispensing database	Level of data collection and aggregation	Data available since:
Austria	Maschinelle Heilmittelabrechnung	Data collected and aggregated nationally	2013
Belgium	InterMutualistich Agenschap–Agence InterMutualiste (IMA-AIM)	Data collection regional/health insurance scheme-level and aggregated to national level database	2006
Czech Republic	National Registry of Reimbursed Health Services (NRRHS)	Data collected and aggregated nationally	2015
Cyprus[3]	Pharmaceutical Services	Not available	2014
Estonia	Prescription Center (SAP SEM platform)	Data collected and aggregated nationally	2010
Finland	Finnish Prescription Registry (Reseptitiedosto) Prescription Centre (Reseptikeskus)	Data collected and aggregated nationally	1993
France	SNIIR-AM	Data collected and aggregated nationally	1999
Ireland	Health Services (Executive (HSE) Primary Care Reimbursement Services (PCRS) database	Data collected and aggregated nationally	1998
Italy	Italian Medicine Agency (AIFA)	Data collection regional/health insurance scheme-level and aggregated to national level database	2012
Latvia	BMANS	Data collected and aggregated nationally	2004
Lithuania	SVEIDRA	Data collected and aggregated nationally	2013
Luxembourg	CNS Prestations	Data collection regional/health insurance scheme-level and aggregated to national level database	1994
Malta	POYC Medicines Approval Database POYC Dispensing database	Data available only in separate databases at the regional/health insurance level	2000
Netherlands	Stichting Farmaceutische Kengetallen	Data collection regional/health insurance scheme-level and aggregated to national level database	2008
Portugal	Prescription database PEM Reimbursement database CCF	Data collected and aggregated nationally	2014

[3] Note by Turkey: The information in this document with reference to "Cyprus" relates to the southern part of the Island. There is no single authority representing both Turkish and Greek Cypriot people on the Island. Turkey recognises the Turkish Republic of Northern Cyprus (TRNC). Until a lasting and equitable solution is found within the context of the United Nations, Turkey shall preserve its position concerning the "Cyprus issue". Note by all the European Union Member States of the OECD and the European Union: The Republic of Cyprus is recognised by all members of the United Nations with the exception of Turkey. The information in this document relates to the area under the effective control of the Government of the Republic of Cyprus.

Country	Name of prescribing/ dispensing database	Level of data collection and aggregation	Data available since:
Romania	SIUI SIPE	Data collection regional-level/health insurance level and aggregated to national level database	2012
Slovenia	Not available	Data collected and aggregated nationally	2001
Sweden	The Swedish Prescribed Drug Registry	Data collected and aggregated nationally	2005
UK (England)	Prescription data: ePact2 Clinical Practice Research Datalink (CPRD)	Individual patient level data from individual general practices are pooled to create a national database.	2014
Australia	Medicare Australia Pharmaceutical Benefit s Scheme (PBS) Claims database	Data collected and aggregated nationally	2002
Israel	Each of the four health insurance funds providing mandatory insurance	Data available only in separate databases at the regional/health insurance level	1995
Japan	National Database of Health Insurance Claims and Specific Health Check-ups	Data collected and aggregated nationally	2011
Korea	Health Insurance Claims Database	Data collected and aggregated nationally	2006
Norway	Norwegian Prescription Database	Data collected and aggregated nationally	2004
Switzerland	Not applicable	Routinely collected data are not collected	Not applicable
United States	Medical Expenditure Panel Survey (MEPS), FDA Sentinel, Medicare, IQVIA	Data available only in separate databases at the regional/health insurance level	1996

Notes: Israel: Patient level data administered by each of the four HMOs; Clalit, Maccabi, Meuhedet, Leumit.
Source: OECD 2018 Survey on routinely collected data

36. For meaningful use in research, databases need to be sufficiently large and representative of the population studied and include all information necessary for the purpose of the study. Most databases include information on the entire population covered by the main health coverage schemes as well as information on all covered goods and services provided to patients.

- In health systems where coverage is based on residence, e.g. Finland, Norway, Portugal, Sweden and the United Kingdom, databases typically cover the whole population, while in health insurance systems, databases only include information on insured people. In countries with multiple insurers, such as Israel, databases may only include information for people insured by a single insurer (e.g. Clalit). Consequently, the proportion of the population captured by databases with routinely collected data on prescribed or reimbursed medicines varies from 80-100% in countries with mandatory and near-universal health coverage.

- Databases storing routinely collected data on medicines usually only capture information on medicines covered and dispensed in outpatient care settings. This means that they generally exclude over-the-counter (OTC) medicines, as well as other medicines not covered or purchased by patients who do not claim reimbursement. In some systems, co-payments per prescription may be higher than the price of the medicine purchased, in which case no reimbursement is made.

3.1.2. Pharmacy records are the main source of routinely collected data, often in combination with personal health records or reimbursement claims

37. Data collection processes have been established to respond to specific needs, which have shaped the structure and content of databases. While pharmacy records are the most frequently used source of routinely collected data on medicines, databases in the responding countries often contain information extracted from a combination of sources including personal health records and reimbursement claims (Table 2).

Table 3.2. Main sources of routine data on prescribed or dispensed medicines in OECD and EU Member States

	Medicines reimbursed by coverage schemes	Medicines prescribed by physician	Medicines dispensed by pharmacists	Medicines dispensed in hospitals	Medicines dispensed in ambulatory care clinics and long term care institutions
Pharmacy records	Cyprus, Estonia, Finland, France, Latvia, Lithuania, Portugal, Romania, United Kingdom	Cyprus, Estonia, Finland, Portugal, Romania, United Kingdom	Belgium, Cyprus, Estonia, Finland, Latvia, Lithuania, the Netherlands, Romania, United Kingdom	Belgium, Cyprus, Romania	Belgium, Cyprus
	Australia*, Norway, United States	Israel, Norway, United States	Norway, United States	Australia*, Israel, Norway, United States	Australia*, Israel, Norway
Reimbursement claims and billing information	Austria, Czech Republic, France, Ireland, Lithuania, Sweden	Ireland	France, Ireland, Lithuania, Sweden		Ireland
	Japan, Korea, Norway, United States	Korea, Norway, United States	Korea, Norway, United States	Korea, Norway, United States	Korea, Norway, United States
Personal health record	Finland, Italy, Lithuania, Luxembourg, Malta, Romania, United Kingdom	Finland, Italy, Malta, Romania, United Kingdom	Finland, Italy, Lithuania, Malta, Romania, United Kingdom	Luxembourg, Malta, Romania	Malta, Romania
	Norway, United States	Israel, Norway, United States	Israel, Norway, United States	Norway, United States	Israel, Norway, United States

Note: *Also includes hospital pharmacy records. Data come from pharmacy records and reimbursement claims are issued by pharmacies, not individual patients
Source: OECD 2018 Survey on routinely collected data

38. Pharmacy records include information on medicines that have been dispensed to patients. For the most part, routinely collected data extracted from pharmacy records include medicines dispensed in outpatient pharmacies. Some pharmacy records include data from hospital pharmacies, e.g. in Australia and Cyprus, while other databases include information on medicines dispensed in long-term care facilities and ambulatory care settings, e.g. in Belgium and Norway. However, routinely collected data rarely cover medicines in hospitals, which is an important gap in information systems.

39. Some countries extend the data collection to also include patient-level information on the prescription and dispensing of specific types of medicines. For example, the Italian Medicines Regulatory Agency (AIFA) carries out ad hoc data collections of some

medicines dispensed in hospitals through the AIFA monitoring registries (Box 3.1). In Slovenia, routine data are collected on very expensive medicines dispensed in hospitals and ambulatory care clinics in order to monitor prescription patterns and use of expensive medicines.

Box 3.1. AIFA Monitoring registries in Italy

The Italian Medicines Agency (AIFA) is the national authority in charge of pharmaceutical regulation and health technology assessments. In 2005, AIFA set up the first monitoring registries of high-cost oncology medicines. Subsequently, the monitoring was extended to include therapies used in cardiology, neurodegenerative disorders, dermatology, ophthalmology, rheumatology, inflammatory diseases, respiratory and neurological diseases. The common feature of monitored therapies is uncertainty related to effectiveness, safety, appropriate use, cost-effectiveness or budget impact (Montilla et al., 2015[11]). In 2017, treatments for diseases affecting the circulatory system accounted for the highest number of monitored therapies, (Aifa, 2018[12]).

Each monitored therapy is registered once a prescription is issued by a physician working in a specialist health centre. Prescribers can follow their patients by monitoring several parameters, such as drug indication, patient benefit of treatment, potential risk and occurrence of adverse events, treatment outcomes.

On the 31st of December 2017, the AIFA registry management network included registered treatments of 1.5 million patients, around 3,500 health facilities, over 32 000 doctors, and 2,300 pharmacists. In total, 49 pharmaceutical companies hold at least one AIFA monitoring registry (Aifa, 2018[12]). The implementation of each product-specific monitoring registry is supported by a contribution from the manufacturer, but market authorisation holders can only access data on their own products. Monitoring registries enable analyses of consumption data and can be linked to other patient-level data, e.g. patient characteristics and clinical outcomes.

The monitoring registries aim to improve early access to innovative therapies, guarantee sustainability and affordability of therapies, collect epidemiological data and monitor appropriate use of several therapeutics. Data included in AIFA's monitoring registries inform the management of medicines in Italy, notably the of Managed Entry Agreements and HTA processes.

40. Data extracted from personal health records are considered a particularly rich source of routine data. Beyond data on prescribed and dispensed medicines, they include longitudinal information on patients' interactions with the healthcare system, diagnostic information, and treatment outcomes. The comprehensiveness of these data by far exceeds that of data available from administrative or research sources and is of great value to monitor and evaluate the performance of medicines and likewise promote quality of care and outcomes (Oderkirk, 2017[9]).

41. More than half the responding countries reported extracting routine data from personal health records, either in combination with reimbursement claims and pharmacy records, or as the sole source of routine data on prescribed and dispensed medicines. In combination with pharmacy records, personal health records enable the study of patient adherence to treatment. Poor adherence to medications affects about half the population

receiving prescription and is estimated to contribute to nearly 200 000 premature deaths in Europe every year (Khan and Socha-Dietrich, 2018[13]). While pharmacy records only capture those prescriptions that are actually dispensed, routine data extracted from personal health records have the potential to capture unfilled prescriptions. This does not produce a perfect indicator of adherence to treatment (filled prescription may not be adequately used), but at least provides some indication of non-adherence.

42. Five of the responding countries use reimbursement claims as the only source of routinely collected data on prescribed and dispensed medicines. Claims and billing information only cover medicines that are included in the range of benefits covered and for which a reimbursement was claimed.

3.1.3. Information on prescribed and dispensed medicines can often be linked with other types of information related to health care consumption

43. Routine databases containing information on prescribed/dispensed medicines often include other types of information, such as diagnoses, use of other health services, etc. If databases do not include this information themselves, it may be possible to obtain it by linking them to other databases. Record linkage involves linking two or more databases using information that identifies the unit of analysis, in this case, the individual patient. Such record linkage often involves using a unique identifier or set of identifiers to merge different sources of data (OECD, 2013[14]).

44. Nearly all responding countries include information on patients' demographic characteristics directly in the routine databases (Table 3.3. Databases containing patient-level information beyond prescribed and dispensed medicines). Beyond patient characteristics, however, routine databases capture only limited information beyond data on diagnosis and survival. The notable exceptions are Malta, Israel and the United Kingdom, where the routine databases also include patients' medical history and test results, and Japan, where details concerning patients' lifestyles and exposure to behavioural risk factors are collected as part of routine health check-ups.

45. In Israel, Clalit Health Services, the largest of the four insurance plans, covering more than 4 million people or about half the Israeli population, maintains an integrated clinical and administrative data warehouse. An internal research institute relies heavily on these routinely collected data to conduct studies of utilisation, safety and effectiveness of technologies. The warehouse comprises electronic data from diagnostic tests, electronic health records used in community primary care clinics and hospitals, medicines dispensed by pharmacies, insurance claims that provide the costs of services, and data recorded in disease registries. A unique identifier for each enrolled member allows Clalit datasets to be linked with both socio-demographic data and the national cancer registry, which are maintained by ministries and government agencies.

46. Reimbursement databases often include information on patients' consumption of other health care services. In Czech Republic and France, for example, data include information on patients' utilisation of all reimbursed outpatient as well as inpatient health services. Furthermore, the French SNIIR-AM database, includes data on hospital stays (diagnoses, surgical procedures, length of stay) (Box 3.2), thus providing insights into different aspects of patients' interactions with the health system.

47. Routine databases can also be linked to other databases containing information on patients' consumption of health services. This linkage concatenates data about an

individual or event that are not available in any single record and can provide researchers with a fuller picture of a patient's pathway through the health care system. For example, the PBS claims database in Australia can be linked to data on utilisation of healthcare services covered by the Medical Benefits Scheme, such as visits to a medical practitioner. In Finland, Latvia and Sweden routine databases can be linked to databases containing information on hospital discharges and outpatient visits.

48. More than half of the responding countries carry out data linkage, most frequently by linking routine databases to death registries and databases containing patients' medical histories. Both are important components that can contribute to a broader understanding of the risks and benefits of treatments delivered to patients. Such databases are used to assess the effectiveness of treatments among larger groups of patients sharing similar characteristics and healthcare needs. Australia, Belgium, Lithuania, Czech Republic, Norway, Sweden and the United Kingdom all link their respective reimbursement and prescription databases to disease-specific registries, e.g. cancer registries. Six responding countries—Australia, Israel, Norway, Romania, Sweden, the United Kingdom and the United States—extend the linkage to data sources that include genetic information.

Table 3.3. Databases containing patient-level information beyond prescribed and dispensed medicines

COUNTRY	DIRECTLY AVAILABLE IN DATABASE								AVAILABLE VIA LINKAGE WITH OTHER DATABASES									
	Demographic characteristics	Prescription-related diagnoses	Other diagnoses	Patients medical history	Results of imaging/lab tests	Lifestyle and health status	Mortality	Health service consumption	Demographic characteristics	Prescription-related diagnoses	Other diagnoses	Patients medical history	Disease registries	Results of imaging/lab tests	Lifestyle and health status	Genetic information	Mortality	Health service consumption
Austria	Y																	
Belgium	Y						Y						Y	Y				
Cyprus																		
Czech Republic	Y		Y	Y				Y					Y				Y	
Estonia	Y	Y							Y	Y	Y	Y					Y	Y
Finland	Y								Y		Y		Y				Y	Y*
France	Y	Y[1]						Y	Y								Y	Y
Ireland	Y						Y											
Italy	Y																	
Latvia	Y	Y					Y		Y		Y						Y	Y
Lithuania	Y	Y							Y	Y	Y	Y	Y				Y	
Luxembourg									Y		Y	Y					Y	Y*
Malta	Y	Y	Y	Y	Y		Y											
Netherlands	Y																	
Portugal																		
Romania	Y	Y							Y		Y	Y		Y		Y		Y
Slovenia	Y											Y						Y
Sweden	Y								Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
United Kingdom	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y

COUNTRY	DIRECTLY AVAILABLE IN DATABASE								AVAILABLE VIA LINKAGE WITH OTHER DATABASES									
	Demographic characteristics	Prescription-related diagnoses	Other diagnoses	Patients medical history	Results of imaging/lab tests	Lifestyle and health status	Mortality	Health service consumption	Demographic characteristics	Prescription-related diagnoses	Other diagnoses	Patients medical history	Disease registries	Results of imaging/lab tests	Lifestyle and health status	Genetic information	Mortality	Health service consumption
Australia	Y								Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Israel	Y	Y	Y	Y	Y		Y		Y**	Y	Y	Y		Y		Y		
Japan	Y	Y	Y			Y												
Korea	Y	Y	Y	Y					Y**					Y	Y		Y	
Norway	Y						Y[2]		Y	Y[2]	Y[2]	Y[2]	Y[2]		Y[3]	Y[3]	Y[2]	Y[2]
United States[4]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y			Y	Y	Y	Y	Y

Note: Cyprus, Portugal do not have patient-level information beyond prescribing/dispensing data; Austria, Cyprus, Ireland, Italy, Japan, Malta, the Netherlands, Portugal cannot link databases). Australia: Linkage can only be done where suitable data are available and is undertaken on a project-by-project basis where suitable approvals are obtained. Belgium: Linkage is possible, but not done on a routinely basis. Linkage may extend to include surveys and financial information. United Kingdom: Clinical data recorded in primary care settings included in the CPRD database *Including social care **Including physiological characteristics. 1. Diagnostic information only covers 31 serious/chronic conditions for which patients are exempted some co-payments. 2. Through linkage with health registries 3. Through linkage to health surveys/population cohorts 4. United States' responses are based on a union of MEPS and Sentinel data.
Source: 2018 OECD Survey on routinely collected data.

Box 3.2. Description of the French National System of Health Data (SNDS)

The SNDS was created in 2016, by aggregating three distinct databases, SNIIR-AM, PMSI and a database on causes of death, which can be linked using a unique patient identifier.[4] The SNIIR-AM and PMSI databases were already linked (Moulis et al., 2015[15]).

1) The SNIIR-AM was created in 2003 with the objective of improving the quality of health care, contributing to a better management of the health insurance system and of public health polices, and to provide feedback to health practitioners as regards their activity, accounts and prescriptions. This database covers all health insurance funds and includes the following information for 65 million persons insured by mandatory health insurance schemes in France:

- Information on patients: age; month and year of birth, gender; coverage by subsidised complementary health insurance where relevant; medical diagnosis justifying exemption from co-payments; department and region of residence; and date of death.
- Information on ambulatory care derived from reimbursement claims includes information on reimbursement amounts and total expenditure, for all healthcare goods and services, i.e. reimbursed medicines (detailed information on the medicine, dosage and box size); medical and dental procedures, identified by codes of the fee schedule (CCAM); biological tests performed, identified by codes of fee schedule (NBAM); medical devices (information on the type of medical device); and health care from other health care professionals, with codes allowing billing but not precise identification of services performed.

2) The PMSI (Programme de médicalisation des systèmes d'information) includes information from hospital discharges, from all public and private hospitals (acute, psychiatric and rehabilitation). For each hospital stay, the database includes: discharge diagnoses (ICD-10 codes): principal, related, and associated diagnoses (up to 30 diagnoses); medical procedures performed during hospital stay (with CCAM codes); date of discharge and length of stay; diagnosis-related groups (DRGs referred to as "Groupe Homogène de Malades") to classify patients in subgroups according to medical procedures and discharge diagnoses for billing purpose; ambulatory visits in hospitals (where relevant); medicines and medical devices included in a specific list of costly medical products paid on top of DRG tariffs.

3) Information on the causes of death, from the Epidemiologic Centre on death causes (CépiDC)

The French government announced the creation of a Health Data Hub in 2019, with an expanded set of information, and enhanced access to datasets (Cuggia et al., 2018[16]).

49. In the Nordic countries, the development of a unique identifier in the 1950s together with a long tradition of population-based health registries has facilitated record linkage across databases as well as national borders (Box 3.3). Since the mid-2000s, each of the Nordic countries has had a national prescription registry that has been used in epidemiological and pharmaco-epidemiological research on the use and effects of medicines.

4 https://www.indsante.fr/sites/default/files/Documents_publics/Rapport_au_parlement_2017_VF.pdf

Box 3.3. Content and potential record linkages of the Nordic Prescription Registries

Altogether, the five country-specific prescription registries in Denmark, Finland, Iceland, Norway and Sweden cover the entire Nordic population of 27 million. The Nordic prescription registries are updated on a monthly basis with the following information:

1) Information on patients

   a. Unique identifier, age, gender
   b. Place of residence
   c. Date of death

2) Dispensed drugs
   a. Unique identifier (Nordic article number)
   b. ATC codes, DDD number, number of packages
   c. Prescribed dose
   d. Reimbursed drugs and non-reimbursed drugs
   e. Date of prescription and dispensing
   f. Diagnosis and indication for use
   g. Generic substitution

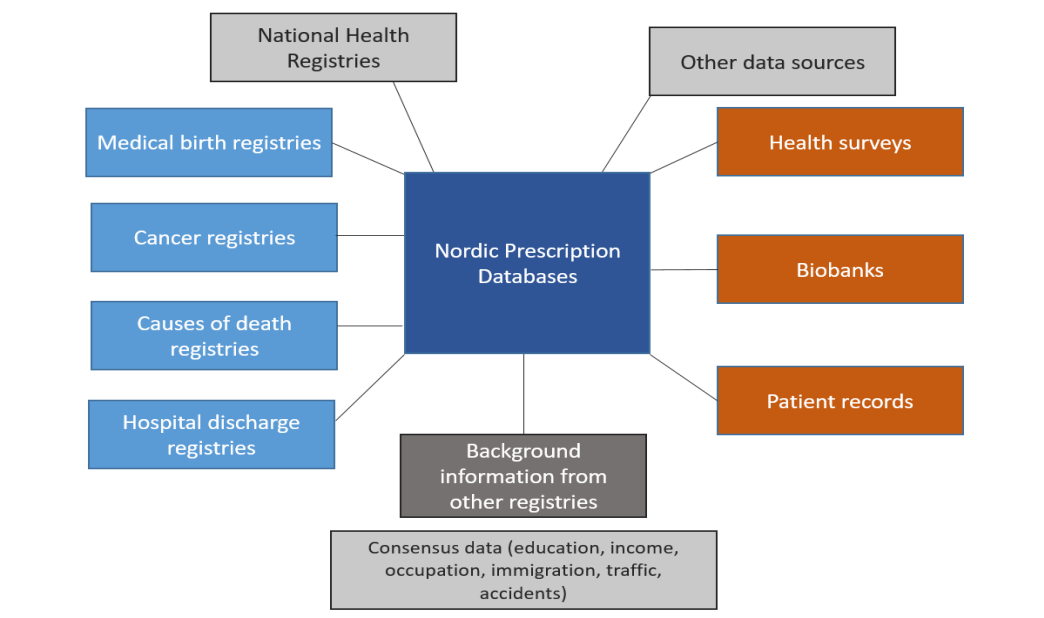
3) Prescriber
   a. Unique identifier, age, gender
   b. Profession and specialty
   c. Practice/clinic/ work place

4) Pharmacy
   a. Unique identifier
   b. Location

The Nordic Prescription Registries do not include the following information:

   a. Non-prescribed OTCs (prescribed OTCs dispensed to chronically ill patients are included)
   b. Medicines prescribed and dispensed in hospitals
   c. Indication for use and prescribed dose not uniformly included across the five Registries
   d. Non-reimbursed medicines not uniformly included across the five Registries
   e. Data on vaccines

Possible linkages between the Nordic Prescription Registries and other databases are illustrated below.



Source: Adapted from (Furu et al., 2010[17])

50. In total, eight responding countries do not link data across databases. Legislative barriers and the lack of unique identifiers are two key barriers to record linkage. In Japan, for example, legislation allows for record linkage but all identifiers are removed from healthcare databases, rendering record linkage impossible (Oderkirk, 2017[9]) (OECD, 2013[14]). However, some of the countries that do not link data already have information beyond the medicines dispensed in their primary routine databases. In Japan and Malta, for example, routine databases containing information on medicines also include broad information on both patients' diagnostic data and outcomes of treatment. Ireland has information on demographic characteristics and mortality, while the Austrian and Dutch databases include data on patient demographics. Routine databases in Cyprus and Portugal do not include data beyond prescribed and dispensed medicines.

3.2. Access to routinely collected data has been restricted, but several countries are moving towards increased openness

51. The 2018 OECD survey on routinely collected data revealed variations in the accessibility of data, with some countries strongly restricting access, even by government or government agencies. In 2018, about half the responding countries reported that routine databases were only accessible to government agencies and employees of the data custodians, who are often the same (the sensitivity of the content.

52. Table 3.4. Beyond the data custodian - who can access routinely collected data on prescribed and dispensed medicines for research purposes?).

53. Reported information on "who can access data" is not easy to interpret. In some countries, such as Italy, Portugal and Norway, a single governmental agency is in charge of marketing authorisation, reimbursement and pricing of medicines, while in other countries, several distinct institutions are involved. In many cases, however, health care payers and all public institutions involved in decision making can access these data.

54. Most countries have a single data custodian. A high level of centralisation in data retention, i.e. having a small number of custodians of national datasets, whether as a result of deliberate policy or default data collection processes, was found to be an advantage in exploiting the value of data (OECD, 2015[8]). Centralisation removes the need to create data sharing agreements between individual custodians, facilitates linkage of datasets generated from different sources, and concentrates resources for data processing and analysis (ibid.). Greater centralisation may enhance data protection because centralised custodians can be resourced to develop the highest levels of data privacy protection, and data are not then held by less sophisticated custodians (ibid.). At the same time, centralisation can arguably also increase risks because a data breach at a large and centralised custodian can be more damaging than when data are more dispersed (ibid.). The use of a unique personal identifier across data generated in different settings is necessary to link datasets and understand care pathways, as well as associations between interventions and outcomes or health care consumption at different levels of the health care system. Similar to centralisation, this greatly increases the value of routine data to research, but also the sensitivity of the content.

Table 3.4. Beyond the data custodian - who can access routinely collected data on prescribed and dispensed medicines for research purposes?

	Data custodian	Ministry of Health or other governmental ministries	The medicine regulatory agency	Health care payers	HTA bodies	Universities and non-profit research units	Other
Austria	Main Association of Austrian Social Security Institutions	y	y	y	y	y	
Belgium	IMA-AIM	y		y	y	y	
Cyprus	Ministry of Health	N/A	N/A	N/A	N/A	N/A	
Czech Republic	National Registry of Reimbursed Health Services – Institute of Health Information and Statistics	N/A	N/A	N/A	N/A	N/A	Access granted to aggregated data upon request
Estonia	Estonian Health Insurance Fund	y	y	y	y	y	
Finland	Social Insurance Institution	y	y	y	y	y	Researchers with approved research proposals
France	National Health Insurance Fund	y	y	y	y	y	Access granted upon authorisation from INDS
Ireland	Health Service Executive				y	y	
Italy	Italian Medicine Agency (AIFA)	y	y				MA holders may access data for their own products
Latvia	NHS	N/A	N/A	N/A	N/A	N/A	
Lithuania	National Health Insurance Fund	y					
Luxembourg	National Health Insurance	y					
Malta	Managing pharmacist of entity	y			y	y	Consultants
Netherlands	Foundation for pharmaceutical statistics	y	y				GPs and organisations linked to the MoH
Portugal	INFARMED	y	N/A	N/A	N/A	N/A	
Romania	National Health Insurance House	y					
Slovenia	National Institute of Public Health	N/A	N/A	N/A	N/A	N/A	
Sweden	National Board of Health and Welfare					y	
United Kingdom	NHS Business Services Authority	y		y			Clinical Commissioning Groups and access granted for approved research proposals

	Data custodian	Ministry of Health or other governmental ministries	The medicine regulatory agency	Health care payers	HTA bodies	Universities and non-profit research units	Other
Australia	Department of Health	y	y	y	y	y	States and territories, general public and the pharmaceutical industry
Israel	Each of the four HMOs	N/A	N/A	N/A	N/A	N/A	
Japan	N/A	N/A	N/A	N/A	N/A	N/A	
Korea	Health Insurance Review and Assessment Service (HIRA)	y		y	y	Y	
Norway	Norwegian Institute of Public Health	y	y	y	y	y	Some data are open and available to the public
United States	U.S. Dept. of Health and Human Services, AHRQ, (MEPS), FDA Sentinel (individual data partners) CMS (Medicare)	y	y	y	y	y	

Note:.N/A: Not available. Israel: Patient level data administered by each of the four HMOs; Clalit, Maccabi, Meuhedet, Leumit. United States: AHRQ: Agency for Health Research and Quality, MEPS: Medical Expenditure Panel Survey; CMS: Centers for Medicare & Medicaid Services.
Source: OECD 2018 Survey on routinely collected data

3.2.1. Sharing health data for secondary use requires good governance

55. Privacy risks that arise from centralised or linked datasets need to be managed with appropriate safeguards. All countries that responded to previous OECD surveys reported having general legislation on data privacy applicable to health and health care data. Some also have laws that govern the use of health care data more specifically. A major problem, however, is that many legislative instruments governing data, privacy and security predate the digital era, and their interpretation in the context of secondary use of electronic health data is difficult, including requirements for informed consent. Many countries have reported legislative barriers to the use of personal health data (OECD, 2013[14]) (OECD, 2015[8]).

56. In 2017, the OECD Council Recommendation on Health Data Governance called upon countries to develop and implement health data governance frameworks that secure privacy while enabling health data use in the public interest (OECD, 2017[18]). These recommendations are not legally binding, but they reflect the political will of OECD countries, and there is an expectation that countries will do their utmost to implement them fully. Over the next two years, the OECD will monitor countries' progress on implementing the Council Recommendation.

57. Data that have been de-identified can generally be made accessible at lower risk to personal privacy. De-identification requires that direct identifiers, such as names or social security numbers, are removed or replaced with pseudonyms that cannot be traced to the underlying individual, and that other variables in the dataset that might allow for indirect identification of individuals are also modified or removed. However, longitudinal patient-level data are at higher risk of indirect re-identification with the increasing follow-up over time, generating patient-specific combinations. Furthermore, as the scope of a dataset gets broader, there is a higher risk of indirect re-identification. To preserve the value of the data for research, it might not be possible in practice to remove all variables that may allow for indirect re-identification and some risk of re-identification usually remains. As a result, de-identified data with a high risk of re-identification are often subject to similar approval

processes as identified data. Also, de-identification often occurs with additional governance measures to create a controlled environment in which data can only be used for approved purposes. Some countries also define different accessibility rules depending on the sector of the applicant, usually with more restrictions for applicants with commercial interests than those from government, universities or non-profit research institutions.

58. Some countries always require the consent of the individual before personal data can be used for research, while other grant exemptions to consent requirements when the use is in the public interest and approved by research ethics boards overseeing the secondary use of the data in question, or where legislation specific to health-related datasets provides for such exemptions. Independent or internal ethics boards review requests for access to datasets who advise custodians or national regulators who make the final decisions on data access requests. Some examples of processes in place to access health data are presented below:

- In **Finland**, access to data generated by the Social Health Insurance Institutions (KELA) is provided for studies that meet certain criteria and comply with the conditions of the Parliaments' Acts on Personal Data (523/1999) and the Openness of Government Activities (621/1999). The Social Health Insurance Institution grants access to its databases following an application process. Applications must be submitted online and be accompanied by an up-to-date research plan providing details of the responsible research institution, type of information requested, the purpose for which the data are needed, a signed confidentiality agreement, and details of the sources of financing. Processing the application takes about 2-3 months and once granted, access is valid for up to five years, though it may be extended via a simplified application process (KELA, 2018[19]). The Finnish Government recently proposed a new act on the secondary use of health and social care data. The main objective of this act is to streamline the processing of data requests, allow access to data faster and improve data security (The Finnish Ministry of Social Affairs and Health, 2018[20]).

- In **France**, the National Institute of Health Data (INDS – Institut National des Données de Santé) provides access to broad datasets for secondary use (INDS, 2017[21]). All data are provided under conditions that guarantee anonymity as decreed by the Council of State following consultation with the national commission on data privacy (CNIL- *Commission Nationale de l'Informatique et des Libertés*). A number of administrations have direct and permanent access to routine data (SNDS) but this information can also be requested for research projects sponsored and performed by other public or private actors, as long as they generate knowledge in the public interest. Following authorisation from the INDS and the National Data Protection Commission (CNIL), the National Health Insurance (CNAMTS) extracts the study population from the National System of Health Data (SNDS) according to the inclusion and exclusion criteria defined by the research organisation. Data are supplied via a secure, electronic medium (Moulis et al., 2015[15]). The Health Data Hub, to be created in 2019, will further expand the set of data available and enhance access to these data (Cuggia et al., 2018[16]).

- In the **United Kingdom**, access to anonymised, patient-level Clinical Practice Research Datalink (CPRD) data for research purposes is subject to approval by the Independent Scientific Advisory Committee (ISAC), which is a non-statutory

expert advisory body. ISAC was established in 2006 by the Secretary of State for Health to provide scientific advice on research requests to access data provided by CPRD. Essentially the ISAC protocol ensures that CPRD data are used for research that does not raise data governance concerns and maintains an acceptable scientific standard. Access to CPRD data is granted by ISAC after completion and submission of an application including information on the purpose of study, the study design, adopted methodology and planned use of the CPRD data, as well as details about the research institution, who will have access to the data, and funding sources. Studies that have been granted access to CPRD data and minutes of` ISAC meetings are publicly available on CPRD's websites (CPRD, 2018[22]).

59. More recently, countries have begun to allow blanket consent to be granted for future secondary use of personal data instead of the more onerous requirements of consent specific to each study. Attention is needed to ensure that individuals are informed about the immediate and potential future use of their data. In some cases, opt-out systems can allow people to withdraw default consent for future use of data from administrative sources. This generally increases the coverage of datasets significantly. While opt-out may be a reasonable solution in some cases, in others it may undermine the objectives of the use of the data and bias the results.

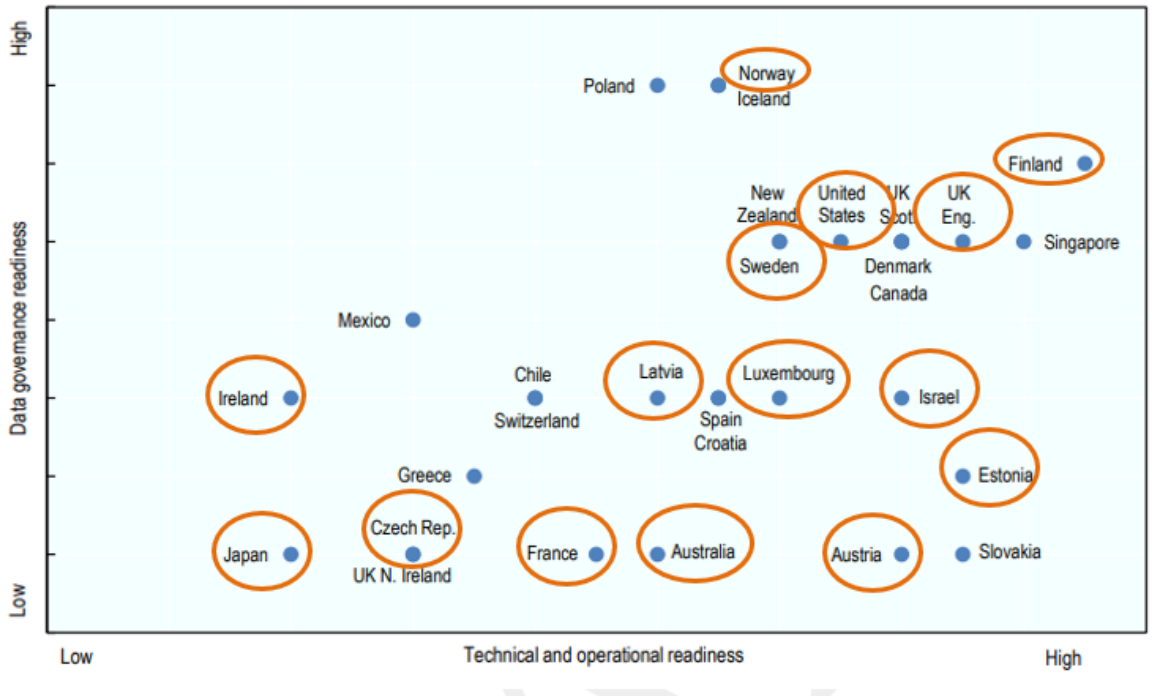
60. OECD recently assessed countries' readiness to further develop health information from personal health records, using information from the survey conducted in 2016 (Oderkirk, 2017[9]). Composite indicators were defined based on basic information, such as having a legal framework and suitable safeguards; extracting data from EHR systems to create national datasets; and using unique identifiers that allow for data linkage. Each country was assigned scores for two dimensions of readiness: governance readiness and technical/operational readiness. These scores are presented in Figure 3.2.

61. Among countries responding to the 2018 survey on routinely collected data (indicated by an orange circle in Figure 3.2), those with the highest cumulative score for technical, operational and data governance readiness for generating health information from personal health records were Finland, Norway and the United Kingdom. Finland held the highest score on technical readiness followed by the United Kingdom. Both countries reported having a robust data infrastructure, standardisation of terminology, and a national system for information sharing among providers. Norway, on the other hand, scored lower on technical and operational readiness, but reported the highest data governance score among the countries that responded to the 2018 survey. This indicates that the legislative framework allows for access to data generated from personal health records for the purpose of secondary use and that the data are used in key monitoring activities within the Norwegian healthcare system. Since these three countries also have personal health records as the main source of routinely collected data on pharmaceuticals, results of the 2016 and 2018 surveys are consistent. Unsurprisingly, these countries provide access to routinely collected data to a wide range of stakeholders who actively use the data in monitoring medicines consumption and prescribing behaviour, and in informing clinical practice, as well as evaluating the effectiveness and cost effectiveness of medicines.

62. Other countries such as Ireland, Japan and France scored comparatively low on all readiness indicators. However, it is important to emphasise that the readiness scores only reflect countries' capacities to generate health data from *personal health records*, and do not take into account opportunities offered by administrative data. Several of the countries that responded to the 2018 survey on routinely collected data on medicines actually extract these data from sources other than personal health records. Interpreting a low readiness

score as a barrier to producing evidence from routinely collected data is therefore partly misleading. Australia, for example, extracts routine data on medicines from reimbursement claims, and use these data actively to inform clinical practice. By contrast, for Japan, the 2018 survey confirmed limited ability to use data generated within the health system to produce evidence. The lack of a national-level unique patient identifier is a major obstacle to the use of longitudinal, person-level data to inform policies or monitor performance.

Figure 3.2. Countries' readiness to generate health data from personal health records



Note: Technical and operational readiness is the cumulative score of nine indicators each valued at one point: EHR coverage, information sharing among physicians and hospitals, defined minimum dataset, use of structured data, unique record identification, national standardisation of terminology and electronic messaging, legal requirements for adoption, software vendor certification and incentives for adoption. Data governance readiness is the cumulative score of four indicators: national plan or priority for secondary data use, dataset creation, and contribution of EHR data to monitoring and research are each valued at one point; and legal issues impeding dataset creation subtracts one point. Orange circle: responding to the 2018 Survey on routinely collected data
Source: (Oderkirk, 2017[9])

3.2.2. Cross-border data sharing presents another layer of challenges

63. The OECD Council Recommendation on Health Data Governance further calls on countries to address obstacles to cross-border data sharing and the European Commission has supported several initiatives aiming to strengthen cross-border availability and use of routinely collected data.

64. In Europe, like in other parts of the world, cross-border access to routinely collected data is challenged by language barriers, data incompatibility, fragmented software structures and systems, and by policies relating to privacy. Several projects and programmes to date have worked to develop cross-border data usage at the European level.

65. The Joint Action on Health Information is a continuation of former health information initiatives. Twenty-eight EU and associated countries have joined this initiative with the aim to streamline health information activities through capacity building, health information tools and political support. The European Medical Information Project (EMIF; ended June 2018), part of the Innovative Medicine Initiative (IMI), developed an approach to standardising health data from ten data sources to the Observational Medical Outcomes Partnership (OMOP) Common Data Model. This mode can accommodate administrative claims databases as well as EHRs, enabling evidence generation from a wide variety of data sources. The concept behind the OMOP Common Data Model is to transform data contained within observational databases into a common format as well as common representation (terminologies, coding schemes, vocabulary). Following the standardisation process, systematic analyses are performed using a standardised methodology based on the common data format. .

66. Building on this work, the public-private European Health Data and Evidence Network (EHDEN) was launched late 2018, with the aim to standardise health data using the OMOP Common Data Model. The project is set up under the framework of Innovative Medicines Initiative 2 and will run from 2018 to 2023. EHDEN will support other IMI2 projects, such as Big Data For Better Outcomes (BD4BO) and collaborate closely with the European Medicines Agency (EHDEN, 2018[17]).

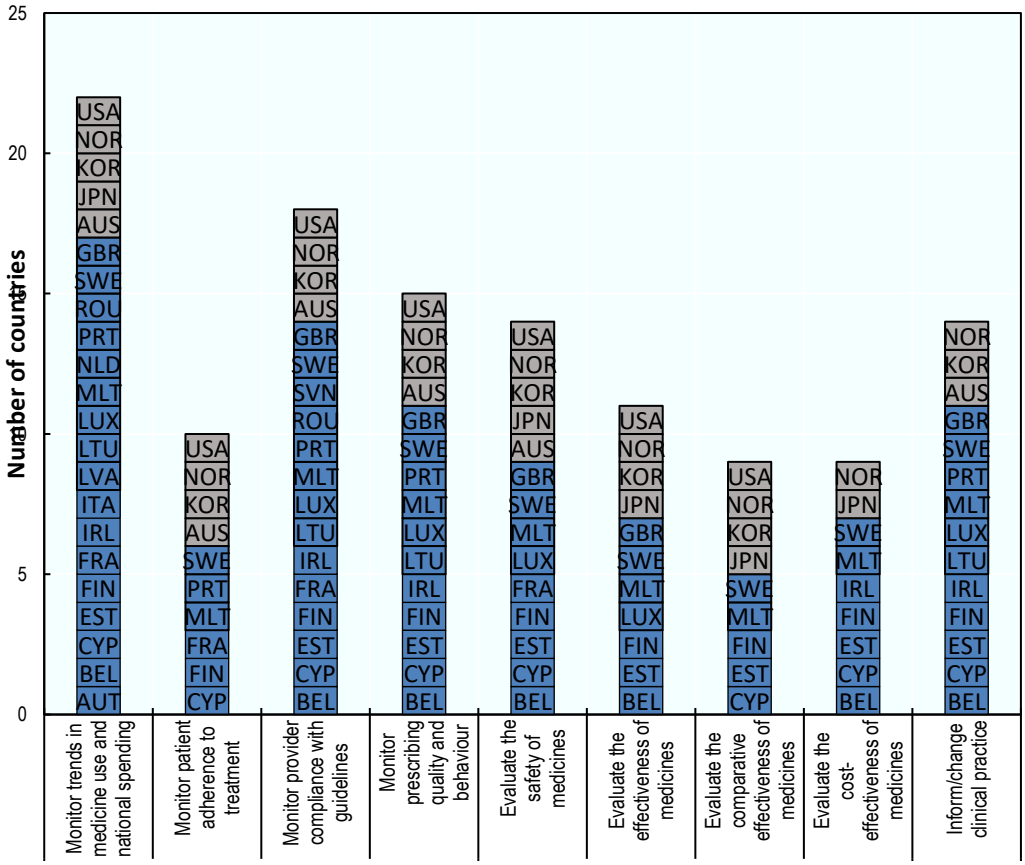
67. EHDEN aims to harmonise clinical data and develop a 21st century ecosystem for real world health research in Europe. The main objectives of the EHDEN consortium are to implement a federated health data network in Europe; enhance the supply and demand side to form a health data eco-system in compliance with robust privacy and ethics governance; and enable the development of new and augmented health services through available and expanded technologies, in the interest of improving health outcomes.

68. At the OECD level, a forthcoming report on Knowledge Based Health Systems will further explore how countries can promote cross-border use of routinely collected data in order to boost knowledge transfer and innovation (OECD, forthcoming).

3.3. Applicability: routinely collected data are mainly used to monitor medicine consumption and prescription quality

69. According to the 2018 survey, routinely collected data on medicines are primarily used to monitor medicine consumption and national level spending (22 countries), provider compliance with guidelines (18 countries), prescribing quality and behaviour (15 countries), and to evaluate the safety of medicines or to inform changes in clinical practice (14 countries) (Figure 3.3). About half the countries that responded to the survey also utilise routinely collected data on prescribed and dispensed medicines in comparative effectiveness and cost-effectiveness analyses. The rest of this section, based on survey responses and desk research, details how countries use routinely data to conduct research on medicines.

Figure 3.3. Routinely collected data are mostly used for monitoring medicine use and spending



Note: Czech Republic: National Registry of Reimbursed Health Services operational since January 2018. Israel and Slovenia: missing information. Italy: response referring to AIFA monitoring registries; United States: The use of data depends on the specific data collection.
Blue colour indicates EU Member States, grey colour indicates non-EU OECD member countries. N=25
Source: 2018 OECD Survey on routinely collected data

70. In the United Kingdom, the CPRD database was initially created for research purposes and is one of the most commonly used data sources in pharmaco-epidemiological research. It harnesses routine data from general practice and produces a primary care dataset, which is one of the largest databases of longitudinal medical records in the world (Herrett et al., 2015[23]). The CPRD database covers a nation-wide sample of 35 million patients, corresponding to a representative sample of the general population. Linking prescription data with patient-level data on hospital episode statistics, disease registries, cancer registries, consultations, hospital discharges and laboratory data makes the CPRD a particularly rich source of routine data. Research and analyses derived from CPRD datasets have provided clinical guidance and best practice for more than 30 years, resulting in over 2,000 peer-reviewed publications investigating drug safety, use of medicines, effectiveness of medicines, health policy, health care delivery and disease risk factors.

71. The Nordic countries have long traditions in registry-based research. The Nordic researchers' network, NorPEN, was established in 2008 in order to facilitate pharmaco-epidemiological research. All Nordic countries use their respective national prescription

registries continuously in post-marketing surveillance of medicines, monitoring of dispensing of medicines and effects of medicines (Furu et al., 2010[17]). Their national coverage and linkage with other national registries and datasets containing information beyond prescription data provide researchers with the opportunity to follow the Nordic population cohort over time and the possibility of capturing and studying rare exposures and outcomes.

72. Most of the published pharmaco-epidemiological studies based on routine data from the Nordic prescription registries concentrate on describing trends in medicine consumption, for example the consumption of warfarin and anticoagulants in Norway and the effects of socioeconomic inequalities on adherence to statin treatment in Finland (Kjerpeseth et al., 2017[24]) (Aarnio et al., 2016[25]). Other types of registry-based research include analytical studies linking medicine utilisation and outcomes. Such studies have demonstrated that elderly persons who receive benzodiazepines are at an elevated risk of developing pneumonia, which is one of several studies investigating medicine safety for the elderly based on routinely collected data from the Finnish Prescription Registry (Taipale et al., 2017[26]). Other studies have examined mortality risks associated with antidepressants and antipsychotics, investigated the association of novel glucose-lowering drugs with the risk of all-cause mortality, cardiovascular disease and severe hypoglycaemia (Danielsson et al., 2016[27]) (Nyström et al., 2017[28]).

73. The similar structures of the Nordic prescription databases facilitates cross-national collaborations, in some cases stretching even beyond the Nordic borders. But et al. (2017[29]) investigated the relationship between the use of certain insulins and the risk of developing cancer based on linked data from prescription and health registries from Denmark, Finland, Norway, Sweden and the CPRD database in England. Another particular strength of the Nordic registries is that they provide longitudinal data, enabling the study of the effects of discontinuation of treatment and trends in medicines consumption over several years, or even decades (Karlstad et al., 2017[30]), (Tiihonen, Tanskanen and Taipale, 2018[31]).

74. Marking the first decade of the Swedish Prescribed Drug Register (SPRD), Wallerstedt, Wettermark and Hoffmann (2016[32]) conducted a systematic literature search quantifying the impact and characterising the scientific output of the SPRD. Between 2005 and 2014, the study identified 338 academic publications based on SPRD routine data. The majority of these studies were analytical (49.1%) or descriptive (29.5%), while the remaining focused on validation (5.9%), health economics (4.7%) or miscellaneous topics (10.7%). The analytical studies investigating exposure to medicines focused on safety (n=49) and/or effectiveness (n=24). Furthermore, over the study period, record linkage using unique personal identifiers increased. The medicines most frequently studied were predominantly used in the treatment of psychiatric conditions (29%) or cardiovascular diseases (20.4%). The systematic literature search clearly illustrates that the nationwide, population-based registry on dispensed prescription medicines made available for secondary use and research has facilitated the development of pharmaco-epidemiological research.

75. Although insurance claims databases are not developed primarily for research purposes, they are often used in pharmaco-epidemiological studies. In France, reimbursement claims data extracted from the SNDS database are used to study how medicines are used and to assess their safety. Between 2007 and 2016, 176 studies based on routinely collected data have assessed medicines or other medical products, accounting for 46.8% of all studies performed with these data (Bégaud, Polton and von Lennep,

2017[33]). Most often, these studies seek to describe product use and exposures of populations to health products (46 studies), to evaluate adverse effects (35 studies), to track misuse (25 studies), to monitor treatment adherence (20 studies) or to monitor compliance with guidelines (20). They have also been used to assess the impact of public health campaigns or public decisions (10 studies) but rarely to assess the effectiveness of medicines (5 studies) (ibid.). Safety of medicines in clinical practice can be assessed from the SNDS or a representative sample of the database, by examining overall mortality and serious adverse events (based on in-hospital discharges, or procedures and drugs used as proxies of diagnoses). These data also allow the assessment of the comparative effectiveness of different treatments.

76. In Korea, insurance claims data from the Health Insurance Review and Assessment Service (HIRA) have been used in research on safety and prescription practices. Studies have examined the association between potentially inappropriate medicine use and hospitalisation, and identified the most common combinations of inappropriate medicine use and adverse outcomes (Jeon et al., 2018[34]). Furthermore, antimicrobial resistance is a major public health concern in Korea, as elsewhere. Based on reimbursement claims, Park et al. (2017[35]) were able to analyse antibiotic use in Korea over a period of seven years and identify the specific types of antibiotics for which utilisation had increased and public health measures should be considered. One of HIRA's core functions is to provide the government with research-based guidance on policy. These studies have been found particularly valuable in informing antibiotic use and prescribing policies.

77. In Australia, routinely collected data are mainly used to monitor medicine use, compliance with reimbursement restrictions and budget impact (see Box 3.5). In Luxembourg, routinely collected data are .used in analyses of national level spending in addition to informing and evaluating clinical practice.

Box 3.4. How routinely collected data are used to monitor medicine consumption in Australia

The Australian Pharmaceutical Benefits Scheme (PBS) is a program of the Australian Government that provides subsidised prescription drugs to all Australian residents. Overseas visitors from countries with which Australia has a Reciprocal Health Care Agreement are also eligible to access the Scheme. It covers a list of medicines dispensed in community pharmacies. The government routinely collects data on subsidised medicines through pharmacy reimbursement claims. The Drug Utilisation Sub Committee (DUSC), a sub-committee of the Pharmaceutical Benefits Advisory Committee (the body responsible for health technology assessment and formulary selection of medicines and vaccines in Australia), monitors the use of subsidised prescription medicines in Australia. DUSC mostly uses routinely collected administrative data, which records the community dispensing of medicines in Australia. The database combines information on PBS-subsidised prescriptions as well as data on prescriptions not subsidised because the full price of the medicine was lower than the applicable patient co-payment. The DUSC analyses the data available and disseminates the information in reports and in its publication Australian Statistics on Medicines, which are available on the PBS website.

DUSC utilisation analysis reports are made publicly available, in order to assist stakeholders including consumers, health professionals, researchers and pharmaceutical sponsors, to better understand how PBS medicines are currently being used, the methods DUSC employs to analyse utilisation of PBS medicines and the PBS data available for these analyses. One study estimated, for example, that approximately 17% of patients of biologic disease modifying anti-rheumatic drugs (bDMARD) may not have trialled methotrexate and sulfasalazine or leflunomide prior to their first bDMARD as recommended in the PBS restriction.

Source: http://www.pbs.gov.au/industry/listing/participants/public-release-docs/2016-02/bdmard-psoriatic-arthritis-addendum%20dusc-prd-2016-02.pdf

78. In the United States, routine data from various data collection initiatives have been used for monitoring medication safety and estimating national level spending. The safety assessment of the Sentinel Initiative resulted in enhanced monitoring of patients on anti-epileptic drugs in order to establish whether these patients were at an elevated risk of developing angioedema. As a result, the drug label was changed, FDA issued safety warnings and published the assessment report on the Sentinel Initiative websites[5]. Routine data from the Medical Expenditure Panel Survey (MEPS) were used to provide a snapshot of expenditure on opioids, those most frequently prescribed, and the sources of payments, including out-of-pocket spending. The analysis identified 152.8 million outpatient opioid prescriptions issued in 2015, corresponding to a total of USD 10.7 billion in outpatient expenditure for adults. Furthermore, the analyses found that two of the most frequently prescribed opioids, hydrocodone and oxycodone, accounted for three-quarters of the spending. While no immediate policy action followed, such analyses are important contributions to inform policy makers and the public on trends in opioid consumption and spending in the United States.

[5] https://www.sentinelinitiative.org/drugs/assessments/aeds-and-angioedema

3.4. Knowledge-sharing could be enhanced

79. This report does not include a systematic literature review of all studies using routinely collected data. Several examples were provided by countries responding to the survey or identified through searches of the peer-reviewed or grey literature (in English or French), including the systematic literature reviews cited above on use of specific databases. Even though this illustrates how routinely collected data are used in some countries, several pieces of information are still absent. In particular, since the routine databases are country-specific and grey literature is often published in national languages, such limits access to research across OECD and EU countries.

80. Access to research based on routinely collected data could be facilitated by establishing repositories, listing all studies and facilitating searches. In the 2018 survey, only five countries reported the existence of a repository of all studies based on routine data. Belgium, for example, l'Agence InterMutualiste and KCE include routinely collected data on prescribed and dispensed medicines in analytical reports that are made publicly available on their respective websites. Similarly, the Netherlands, Norway and the United States publish studies and reports on websites, making the assessments and analyses available to relevant audiences, including persons involved in pharmaceutical policy making, and pricing and coverage decisions. However, this does not guarantee that information is optimally shared across countries, regulators, assessment bodies or decision-makers.

81. The creation of an international repository of research based on routinely collected data would potentially fill a gap in the current knowledge base. First, language barriers would be overcome by providing translations of non-English language research, especially for those reports not indexed in peer-reviewed literature. Second, including studies performed to assess the performance of medicines would be useful for informing clinical guidelines and best practice across countries. Internationally available data could also pave the way for cross-country collaboration and comparison, as it would raise awareness of research based on routinely collected data and clinical practice in other countries.

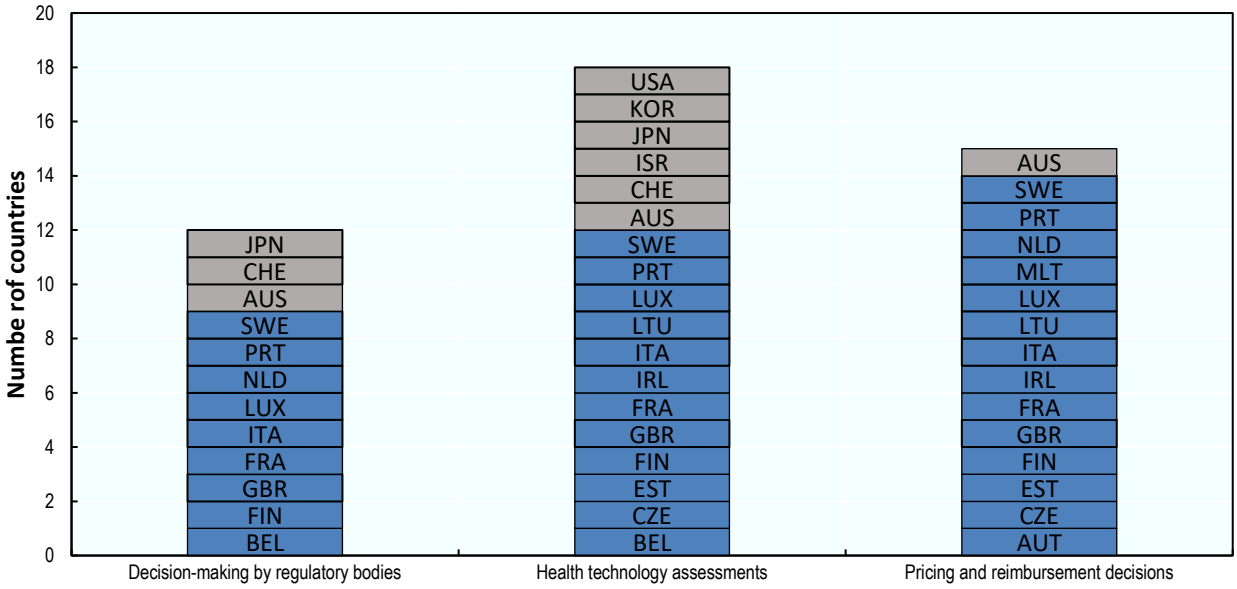
82. Building such a repository however, would require a significant investment from countries to gather all conducted studies based on routinely collected data, without clear identification of which institution would be responsible for this task. In addition, it would duplicate existing databases for scientific publications that are already indexed.

83. One option to increase cross-border knowledge sharing would be to increase the number of scientific publications derived from these studies. This objective could be reached by facilitating access to data for researchers or by providing other institutions producing these studies (e.g. health insurance funds) with incentives to publish them in peer-reviewed scientific journals. A scientific publication increases the diffusion of results –especially if it is open access- and provides a certain expectation of reliability. This is a long and costly process, which might require training and support for the staff of these institutions. Such efforts could focus on new knowledge which sounds particularly relevant and actionable (likely to influence clinical practices for instance) and generalisable to other contexts.

4. Actionability of evidence from clinical practice: from monitoring to policy impact

84. While available and accessible routinely collected data are increasingly being used in research, evidence derived from such research plays a limited role in the management of pharmaceuticals and decision-making processes. According to the 2018 OECD Survey on routinely collected data, a number of countries are now using evidence from clinical practice in HTA and post-marketing assessments, and to guide decisions on pricing and reimbursement (Figure 4.1). However, most surveyed countries employ an evidence hierarchy, which grades evidence from RCTs more highly than that derived from clinical practice. Evidence from clinical practice plays more of a supporting than a central role in decision-making.

Figure 4.1. Countries where routinely collected data and evidence from clinical practice are taken into account in assessments or decision-making



Note: The figure includes countries where routinely collected data are considered or may be considered in assessments and decision-making processes. Missing information: Cyprus, Norway, Slovenia. Blue colour indicates EU Member States, grey colour indicates non-EU OECD member countries.
Source: 2018 OECD Survey on routinely collected data

85. Researchers of the GetReal consortium, part of the Innovative Medicines Initiative (IMI) funded by the European Commission, recently reviewed policies and activities related to evidence from clinical practice on the safety and effectiveness of medicines in Europe and the United States (Makady, Goettsch and Willemsen, 2015[36])[6]. This review

found that studies of comparative effectiveness for conditional reimbursement and conditional payments are the most frequent contexts in which evidence from clinical practice is used, followed by regulatory assessments. However, little information is currently available from public sources on the policies of payers regarding the use of evidence from clinical practice in decision making related to health technologies.

86. This section explores how routinely collected data have been used in post-marketing studies and health technology assessment, and the extent to which these data and evidence have influenced pricing, reimbursement decisions, and clinical practice. Each subsection presents a set of case studies demonstrating how routinely collected data and evidence from clinical practice have guided decision-making. The final sub-section outlines the main barriers faced by countries to using routinely collected data and generating evidence from clinical practice.

4.1. Regulators and health systems use routinely collected data for post-market studies

87. By definition, regulatory agencies can only use evidence derived from data collected in *routine* clinical practice after the initial marketing authorisation of a new technology because such data do not exist before the introduction and diffusion of the technology. Regulators in the EU and across OECD countries thus rely on data from clinical practice mainly in post-market safety surveillance.

88. However, regulators may sometimes also require that evidence from routine data be generated to confirm the assessment of an initial marketing authorisation.[7] Regulators typically require market authorisation holders to conduct post-authorisation studies or to establish registries when circumstances favour an initial marketing authorisation despite uncertainty about the risk/benefit balance offered by the new medicine. This can be the case, for instance, when a new treatment has the potential to address a significant unmet need or alleviate a particularly severe disease for which no treatment alternatives are available, but for which RCTs have not yet fully demonstrated the degree of efficacy of the treatment or provided evidence of longer-term effects. To date, the FDA has used evidence from clinical practice to support the approval of New Drug Application (NDA) submission for rare diseases or in small populations (FDA, 2017[37]). Routine data collected and analysed after the initial marketing authorisation may then be used for subsequent reassessment of safety or effectiveness (Makady, Goettsch and Willemsen, 2015[36]).

89. Increasingly, regulators also take into account evidence from clinical practice to assess the efficacy of new medicines when RCTs are impossible or unethical to conduct. Cancer, paediatric conditions and orphan diseases are particular areas where evidence from clinical practice may be used to inform the assessment of efficacy. Recent legislative changes in the United States, for example the 21st Century Cures Act which became federal law at the end of 2016, provided for the establishment of a program to evaluate the potential use of "evidence from clinical experience" to support marketing authorisation and post-approval requirements (Upton, 2015[38]). To implement the law, in December 2018 the FDA announced a strategic framework to enhance the integration of evidence generated

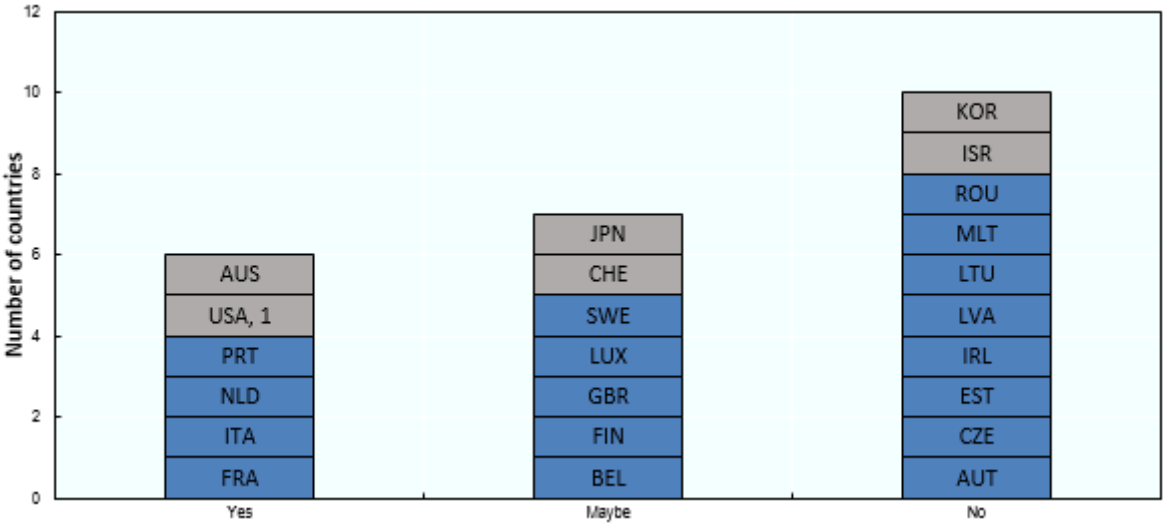
[7] EMA Marketing authorisations are valid for 5 years; see https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-procedural-qa/renewal-annual-re-assessment-marketing-authorisation#renewal-of-marketing-authorisation-section)

from routine data into regulatory decisions. Among other purposes, the framework outlines use of such evidence for approval of new indications for already approved drugs, to support revisions to product labelling on effectiveness or safety, and adding comparative effectiveness or safety information (FDA, 2018[39]). The scope of the framework covers data derived from electronic health records; medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices (ibid.).

90. Prior FDA guidance on studies using routinely collected data did not mandate data sources or study designs, stating that these should be chosen on a case-to-case basis as appropriate for the treatment in question and the hypothesis to be tested (Makady, Goettsch and Willemsen, 2015[36]). This principle is maintained in the current framework (FDA, 2018[39]). The framework also acknowledges, in particular, that it remains methodologically difficult to infer a causal treatment effect using observational study designs and that the FDA will "evaluate the potential role of observational studies in contributing to evidence of drug product effectiveness" (ibid., p.12). Similarly, EMA guidance on post-authorisation efficacy studies states that study design should be chosen based on the particular product and the type of uncertainty to be addressed, ensuring that the study "will be feasible, ethically acceptable and of a design known to return reliable and interpretable results in relation to the primary objectives" (EMA, 2016[40]). Most registry requirements issued by the EMA concern safety of orphan drugs or medicines approved under "exceptional" circumstances (Cave, 2016[41]).

91. About half the responding countries reported that regulatory agencies take into account evidence from clinical practice are or may be included in their assessments (Figure 4.2). In Italy, routinely collected data and evidence from clinical practice are used for post-marketing monitoring of vaccines, orphan drugs and specific medicines, while in Portugal evidence from clinical practice is used for pharmacovigilance. Further details of how the European Medicines Agency, the French Medicines Agency (ANSM), and the US Federal Drug Agency (FDA) have used evidence from clinical practice in post-market surveillance are provided in case studies below as well as in Annex 2.

Figure 4.2. Countries reporting on how regulatory agencies take into account routinely collected data in their assessments and decisions



Note: Missing information: Cyprus, Norway, Slovenia. 1 Only Sentinel data are used for post-marketing assessments. Blue colour indicates EU Member States, grey colour indicates non-EU OECD member countries.
Source: 2018 OECD survey on routinely collected data

The European Medicines Agency

92. Studies based on data from clinical practice are a part of pharmacovigilance processes. To inform reviews of the safety profiles of approved medicines, the EMA conducts studies based on evidence from clinical practice of drug utilisation and adverse outcomes using various databases fed by electronic health records (EHR), insurance claims, and outpatient prescriptions. These reviews are governed by European Union legislation and are triggered when the competent authority of a member state, the European Commission, or a market authorisation holder notifies the EMA of a quality, safety or efficacy issue (EMA, 2018[42]); (European Parliament and Council, 2001[43]). The EMA then conducts a scientific review of all available evidence, including studies based on registries or routinely collected data sources, sends its opinion to the European Commission for adoption of a legally binding decision addressed to all member states. Such decisions may lead to restrictions or amendments of the market authorisation(s), for example through the addition of contradictions to update the product information.

93. For example, in 2014 Estonia informed the EMA, pursuant to Article 31 of Directive 2001/83/EC, of its concerns about the cardiovascular risks associated with testosterone therapy (TT), and the need for a European review to evaluate the impact of the risk of cardiovascular events on the overall benefit-risk profile of testosterone-containing products. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA noted that the available data on the cardiovascular risks associated with testosterone therapy (TT) came mainly from observational studies (EMA, 2014[44]). In its review, PRAC considered eight published articles reporting results of studies on safety, of which five were observational studies using routinely collected health care data, two were systematic reviews of RCTs, and one was an original RCT, as well as data from a European registry (RHYME). PRAC also considered three studies of efficacy, none of which were based on routinely collected data. In addition, the review considered a study of testosterone

prescribing patterns conducted by researchers at the EMA, using routine data from the United Kingdom. The PRAC concluded that the findings in the literature did not show an increased risk of cardiovascular events consistently, and did not corroborate the putative signal of an increased risk associated with testosterone therapy. The PRAC recognised, however, that testosterone may cause severe complications in some patient sub-groups, and that some uncertainty remained as to the direct and indirect effects of testosterone on the cardiovascular system in general and in patients over 65 years of age, which should be investigated further. The PRAC requested that the market authorisation holders continue to monitor cardiovascular events and report findings of ongoing studies in their Periodic Safety Update Reports, and that updates to the product information should be made to ensure that potential cardiovascular risks associated with testosterone use were addressed in all approved products (EMA, 2014[44]).

94. The EMA conducts studies using routinely collected data mainly for pharmacovigilance but also for assessing drug utilisation and disease prevalence. Through commercial contracts, the agency has access to the UK Health Improvement Network (THIN) and IQVIA[8] databases as the main sources of routinely collected data. The IQVIA databases provide anonymised electronic medical records (EMRs) collected from primary care practices and office-based specialists in France and Germany. These include demographic information, insurance status, primary diagnoses and co-morbidities, medical histories, referrals, information on prescriptions, non-pharmaceutical treatments, and treatment costs. Datasets are updated monthly. In France, data cover some 1,100-physician practices, 4.4 million patients and 126 million prescriptions from 1997 to the present. In Germany, data cover some 2,700 practices, 32.2 million patients and 303.2 million prescriptions from 1992 to the present (personal communication with IQVIA Institute for Human Data Science). The THIN database centralises EHRs from more than 500 UK-based primary care practices, comprising, among other information, socio-demographic data, details of consultations, test results, diagnoses and referrals to hospitals and specialists and prescriptions of some 11 million patients (UCL, 2017[45]). In addition, the EMA may commission external studies to access other datasets via academic institutions (personal communication with Alison Cave, EMA).

95. Since 2014, the EMA has been piloting an adaptive pathway to accelerate approval and patient access to treatments in areas of high-unmet medical need "where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine" (EMA, 2018[42]). This process typically entails an initial marketing authorisation, targeting a narrow group of patients likely to benefit most from the treatment, and iterative phases of evidence gathering and licensing adaptations to expand use to a wider patient population as more data become available. Although the use of evidence from clinical practice to supplement RCT data was a focus of the pilot, proposals from applicants for market authorisation relied mainly on registries and the EMA subsequently concluded that evidence from clinical practice played a limited role in licensing decisions (EMA, 2016[46]).

Australia

96. The Therapeutic Goods Administration (TGA) is the agency responsible for the regulation of human therapeutic products in Australia. The TGA conducts pre-market assessments, issues marketing authorisations for therapeutic goods including medicines

[8] The IMS Institute is now the IQVIA Institute for Human Data Science

and vaccines, and undertakes pharmacovigilance. In 2018, when TGA's Advisory Committee on Medicines was asked to provide advice on the safety of sodium valproate in pregnancy and women of childbearing age, routinely collected data on reimbursement claims and evidence from clinical practice were used to inform the analysis. Valproate is approved for indications such as epilepsy and mania in bipolar disorder patients. However, exposure to valproate during pregnancy considerably increases the risk of malformation and developmental problems for the foetus. An ongoing review in Europe studied the effectiveness of risk mitigation activities to inform patients and health professionals of the risk of malformations with increasing doses of valproate. The Advisory Committee on Medicines recommended stronger risk mitigation measures, and educating providers about appropriate prescribing—including avoiding the use of valproate in women of childbearing age for all non-seizure indications and always using the lowest effective dose. The effect of these actions will be reviewed in two years.[9]

France

97. In France routinely collected data have been used on several occasions for post-market surveillance.

- The assessment of risks associated with benfluorex is a well-known example. Motivated by safety alerts, experts used the French routine databases on health insurance claims (SNIIRAM) and hospital discharges (PMSI) to assess a potential link between benufluorex and the risk of valvular heart disease. All patients identified with reimbursement for anti-diabetic medicines and/or insulin and hospitalised diagnosed with valvular insufficiency were included in the study. The study showed a statistically significant association between benfluorex in diabetic patients and hospitalisation for valvular heart disease in the 2 years following exposure to benfluorex (Weill et al., 2010[47]). As a result, benfluorex was withdrawn from the French market.
- In 2011, a study of two products containing pioglitazone was conducted to assess the risk of bladder cancer, using administrative data (SNIIR-AM). The study confirmed the results of earlier clinical studies suggesting an elevated risk, and the French regulatory agency (ANSM) suspended the marketing authorisation of the products (Cnamts, DSES and DESP, 2011[48]). The EMA, however, maintained the marketing authorisation, leading ANSM to reverse its decision.
- In 2015, the ANSM and the main health insurance Fund (CNAMTS) also conducted a study to assess whether exposure to HPV vaccine was associated with the onset of 14 types of autoimmune diseases. The observational cohort study included 2 256 716 girls, one third of whom had been vaccinated (93% with one of the two available vaccines). The study concluded that vaccination was not significantly associated with the onset of 12 of these diseases, but could not reject the hypothesis of an association with two diseases: chronic inflammatory bowel disease and Guillain–Barré syndrome (ANSM/CNAMTS, 2015[49]).

9 https://www.tga.gov.au/sites/default/files/acm-meeting-statement-meeting-9-31-may-1-june-2018.pdf

United States and the Sentinel Initiative

98. Monitoring post-marketing safety is a major part of the FDA's remit. Sentinel is the FDA's national electronic system for monitoring the safety of FDA-regulated medical products, including drugs, vaccines, biologics, and medical devices. It was launched in 2008 following the passage of legislation requiring the development of a system for active post-marketing risk assessment and analysis for medical products. Development took place in collaboration with public, academic, and private entities, to establish procedures for obtaining access to disparate data sources and validated methods for the creation of a system to link and analyse data from multiple sources. The project harnesses information from multiple EHR systems, administrative data and insurance claim records – these data include demographics, enrolment history, drug dispensing, encounters, vital signs, lab results, diagnoses, procedures, and mortality.

99. The Sentinel System was designed to augment, but not replace FDA's existing post-market safety monitoring systems. For many years, various parts of FDA have gathered risk information about drugs and other medical products through programs that rely on external sources (such as product manufacturers, consumers, patients, and health care professionals) to report suspected adverse reactions, such as its Adverse Event Reporting System. This type of safety monitoring is known as "passive surveillance." In contrast, the Sentinel System has been designed as an "active surveillance" system, because the FDA can initiate its own safety evaluations that use available electronic health care data to investigate the safety of medical products.

100. In one notable example, FDA pursued an investigation of influenza vaccine safety in 2013-14. This required refreshing the data more frequently (previously on a quarterly basis) to inform timely regulatory decisions about the use of influenza vaccine. Yih and colleagues (2016) monitored the risk of two health outcomes, anaphylaxis and seizures, conducting sequential analyses within 6 weeks of the last care-date in the dataset. A total of 6 682 336 doses of inactivated and 782 125 doses of live influenza vaccines were captured. The primary analyses did not identify any statistical signals, although a secondary analysis revealed a higher risk of seizures that is undergoing further investigation (Yih et al., 2016[50]).

101. While during early Sentinel development there was a concern regarding transparency – i.e., when to communicate a potential safety signal to the public – the pilot was generally considered a success and transitioned from Mini-Sentinel to the full Sentinel System between 2014 and 2016. Some areas where active surveillance was specifically cited as complementing previous passive surveillance efforts included expanded access to subgroups and special populations (e.g., the elderly), access to longer term data, and adverse events occurring commonly in the general population (e.g., myocardial infarction, fracture) that tend not to get reported to FDA through its passive reporting systems.

102. Looking forward, the FDA has expressed its intent to use the Sentinel infrastructure for other purposes than safety surveillance. A system is currently being developed to actively gather information about product performance. Officials have noted that Sentinel could also be used to study the effects of switching between branded and generic medicines. On the device side, Sentinel could help cement a national evaluation system for medical devices, but unique device identifier (UDI) integration in EHRs and insurance claims forms remains a challenge. FDA envisions that the Sentinel System will become part of a larger national partnership that will meet the needs of regulators as well as others including health care systems, academicians, and the industry.

103. For medical devices, the FDA has set out objectives to gain access to clinical registries, claims data, and EHRs, and to increase the proportion of pre- and post-market regulatory decisions on the basis of evidence from clinical practice (FDA, 2018[51]). Draft guidance on the use of such evidence to support regulatory decisions for devices was published recently (FDA, 2016[52]). This document applies the same principles to selection of data sources and study designs as for medicines but considers a wider scope of routinely collected data and specifies that evidence from clinical practice may be used, among other purposes, to (pp.9-10):

- Generate hypotheses for prospective clinical studies;
- Provide historical control groups or, in settings where a registry or some other systematic data collection mechanism exists, concurrent control groups in clinical studies to support device approval;
- In some circumstances, where devices are routinely used in a broader patient population, expand the labelling to include additional indications for use or update the labelling to include new information on safety;
- Conduct routine post-market surveillance to understand the evolution of benefits and risks and identify safety signals, and for post-approval studies imposed at the time of device approval.

4.2. Health technology assessment could benefit more from routinely-collected data

104. HTA agencies typically produce assessments of the comparative efficacy, effectiveness and cost-effectiveness of technologies, which may inform reimbursement decisions or price negotiations with manufacturers. While HTA agencies do not always have clear policies or guidelines on the use of evidence from clinical practice in particular, they generally aim to consider the entire evidence base available at the time of assessment, and may therefore include evidence generated in clinical practice (Makady, Goettsch and Willemsen, 2015[36]). This implies that the type of evidence that may be considered is dependent on the timing of the assessments, which may occur before initial reimbursement decisions, or afterwards to evaluate cost-effectiveness in practice, determine pricing, or update conditional reimbursement conditions (Makady et al., 2017[53]). In Germany and England, for example, new technologies, including new medicines, are in principle reimbursed and available to patients upon marketing approval, and assessments occur after the technology has already been introduced in clinical practice. By contrast, France and the Netherlands assess newly approved medicines upfront before coverage is determined and prices set (van Nooten and Caro, 2013[54]). As a result, evidence from clinical practice can only become available after the initial assessment and be considered in subsequent reassessments.

105. Most HTA agencies employ a formal hierarchy of evidence and attach lower weight to observational studies that do not control for bias through randomisation (Makady et al., 2017[53]); (Makady, Goettsch and Willemsen, 2015[36]). HTA agencies are generally circumspect in considering evidence from clinical practice in their effectiveness assessments, and do not estimate effectiveness based on such evidence alone. However, evidence from clinical practice can be considered reliable for estimating other parameters of interest, such as measures of disease epidemiology, utilisation of technologies and treatments, or resource consumption (costs) (ibid).

106. The European Commission has launched several initiatives in order to support HTA agencies in strengthening methodologies to better integrate evidence from clinical practice in their economic evaluations:

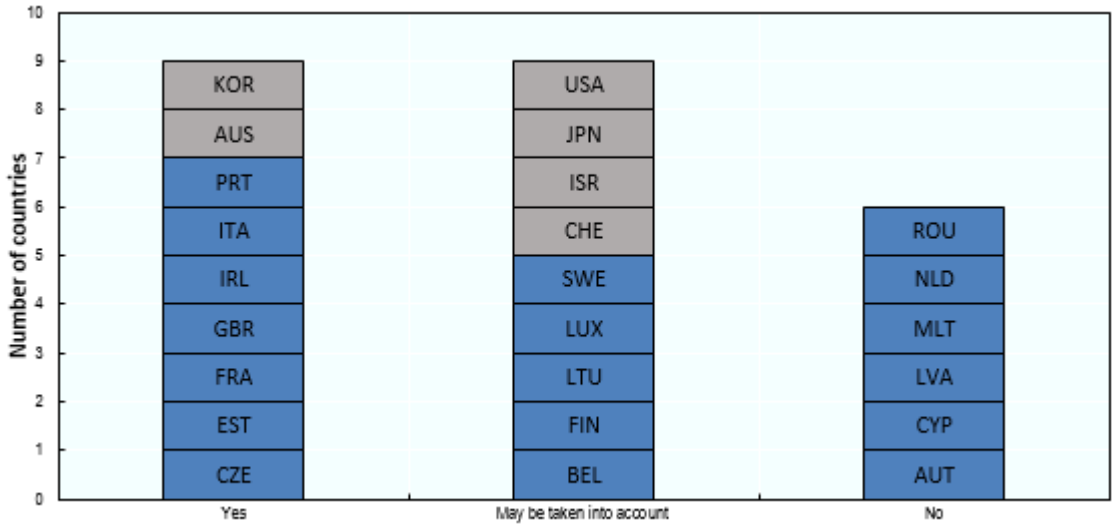
- Across ten identified research areas, the IMPACT HTA[10] project aims to integrate clinical and economic data from different sources, to improve the methodology for conducting economic evaluation in HTAs. One of the research areas will specifically concentrate on developing a tool to combine and use RCT and observational data, including routine collected data, in economic evaluations.
- The ProgrammE in Costing, resource use measurement and outcome valuation for Use in multi-sectoral National and International health economic evaluAtions (PECUNIA) aims to develop new standardised, harmonised and validated methods and tools for the assessment of costs and outcomes in European healthcare systems.[11]
- Taking HTAs a step into the future, the HTx project was launched in January 2019. HTx' overall objective is to create a framework for the next generation of HTA. Working in close collaboration with EUnetHTA, HTx will facilitate the development of methodologies to deliver more customised information on the effectiveness and cost-effectiveness of complex and personalised combinations of health technologies, including Artificial Intelligence and Machine Learning systems.

107. According to the survey, countries often take into account evidence from clinical practice in HTAs (Figure 4.3). Nevertheless, the evidence hierarchy prevents routinely collected data from being central to decision-making, but rather playing a supporting role in evaluations and assessments. Examples of policies and assessments based on routine data and evidence from clinical practice in Estonia, Finland, France, Germany, Ireland, the United Kingdom and the United States are provided in the paragraphs below.

[10] https://www.impact-hta.eu/

[11] https://www.pecunia-project.eu/

Figure 4.3. Countries reporting that HTA agencies consider routinely collected data in their assessments



Note: Missing responses from: Germany, Slovenia, Norway. There is no HTA agency in Cyprus. Blue colour indicates EU Member States, grey colour indicates non-EU OECD member countries.

Source: 2018 OECD survey on routinely collected data.

Estonia

108. The Estonian Centre for Health Technology Assessments was established in 2012 and has since developed HTA methods relevant for the Estonian healthcare setting and carried out several HTAs. Routinely collected data on prescribed and dispensed medicines and evidence from clinical practice are considered in the evaluations. Results from the HTAs inform the Estonian Health Insurance Fund in their coverage decision-making processes, and support the Ministry of Social Affairs in making decisions on the reimbursement of pharmaceuticals and the funding of public health interventions. Furthermore, the recommendations and conclusions arising from the HTAs inform and in some cases motivate changes in medical practice and clinical guidelines.

France

109. The Transparency Commission (CT) of the French High Authority for Health (HAS) is charged with evaluating the efficacy and added therapeutic benefit of all newly approved technologies. This assessment informs reimbursement decisions by French statutory insurance and price negotiations with manufacturers. The CT may require post-reimbursement studies when uncertainty as to the benefits of a technology is high at the time of the initial assessment, and re-evaluates all reimbursed technologies at 5-year intervals (HAS, 2015[55]) (van Nooten and Caro, 2013[54]). In parallel to the clinical effectiveness assessment carried out by the CT, the HAS conducts a cost-effectiveness assessment for selected products. Conclusions from the assessments are used by the committee in charge of pricing (CEPS) in price negotiations with manufacturers.

110. While post-reimbursement studies most often rely on studies conducted by manufacturers, the CT recognises that routinely collected data can be used and considered, although interpretation of the evidence should be cautious. The guidance further states that

there is no preferred study design, but that data sources, study design and corresponding methods must be justified in the context of each study, and should minimise the potential for bias.

111. In its periodic or ad-hoc re-assessments of medicines, the CT has considered studies by public research institutions that used routine data. A few examples are provided below:

- Following the 2011 study confirming the association between the use of pioglitazone and bladder cancer (Cnamts, DSES and DESP, 2011[48]), the CT re-assessed the therapeutic value of one product containing pioglitazone and considered it was insufficient to warrant continued reimbursement.
- Routine data have also been used to re-evaluate the impact of exposure to isotretinoin during pregnancy (Rouzès and Jonville-Béra, 2014[56]). Although teratogenic effects are well-known and expected to be averted (e.g. through prescription conditions), routine data show that pregnant women continue to be exposed to these products, confirming the need for a strengthening of practice guidelines and risk management plans.
- In 2013, another study using routinely collected data revealed over- and misuse of benzodiazepines in France (ANSM, 2013[57]) . This triggered a re-evaluation of all benzodiazepines by the Transparency Commission, which downgraded their assessed therapeutic value. This subsequently led to a decision to reduce their reimbursement rate from 65% to 15%.[12]

Germany

112. The German Institute for Quality and Efficiency in Health Care (IQWiG) is charged with health economic evaluation of medical interventions in general, and of the costs and benefits of drugs reimbursed by the statutory health insurance scheme in Germany in particular. Subsequent to marketing approval and reimbursement of new medicines, IQWiG evaluations determine reimbursement prices by comparing their effectiveness to alternatives available on the market (van Nooten and Caro, 2013[54]). IQWiG recognises that the external validity of RCT-based evaluations is limited but that this does not justify substituting RCTs with observational RWD, and that more rigorous studies reflecting everyday conditions, such as pragmatic clinical trials, are desirable and feasible. The Institute thus strongly favours RCTs in assessing the clinical benefit of new medicines , as mandated by legislation (Wenzl and Paris, 2018[58]). A review of single-technology assessments by IQWiG in 2015 found that evidence from studies other than RCTs was not considered (Griffiths and Vadlamudi, 2016[59]). Methodological guidance further states that hierarchies based on study design are not an ideal means by which to assess the quality of evidence, and a formal methodology is applied to assess the risk of bias of all randomised studies found relevant to the technology assessed (IQWiG, 2015[60]). The Institute does not apply a hierarchy to rank different designs of observational studies and does not estimate the risk of bias in study results, noting that "their results generally carry a high risk of bias due to the lack of randomization" (ibid, p.147).

12 https://www.legifrance.gouv.fr/jo_pdf.do?numJO=0&dateJO=20141114&numTexte=107&pageDebut=19211&pageFin=19213

Ireland

113. Different public bodies and research groups undertake HTA in Ireland. The National Centre for Pharmacoeconomics carries out cost-effectiveness assessments of medicines while the Health Service Executive assesses clinical and cost-effectiveness of medical devices. Pharmaceutical companies undertake HTA in preparing applications for reimbursement, and some academic groups undertake HTA for research purposes. Based on these HTAs, the Health Information and Quality Authority (HIQA) informs national-level policies.

114. The HIQA posts the results of the HTAs as well as the HTA reports on its website. Several examples exist where routinely collected data have been taken into account and influenced HTAs carried out by HIQA. In 2017, for example, HIQA based its assessment of smoking cessation treatments on routinely collected data from the Health Service Executive - Primary Care Reimbursement Service (HSE-PRCS) database, and recommended that the uptake of varenicline should be maximized, alone or in combination with nicotine replacement therapy, among smokers wishing to use some type of pharmacological support to quit smoking. When concerns regarding over-prescription were raised**,** HSE-PRCS data were used to monitor prescribing behaviour and compliance with guidelines.

The Netherlands

115. In the Netherlands, the Ministry of Health, Welfare and Sports bases their reimbursement decisions on effectiveness and cost-effectiveness assessments carried out by the Dutch Health Care Institute (ZIN). ZIN states that evidence generated in RCTs is the most reliable and carries the most weight in assessments. However, it also recognises that RCTs are not always feasible and are not always reflective of routine clinical practice, thus a framework is applied to grade the reliability of evidence according to the potential for bias and to determine what can serve as 'appropriate evidence' for the intervention concerned (ZIN, 2015[61]). Guidance on cost-effectiveness analysis uses the same framework and states that observational studies are an acceptable source of evidence (ZIN, 2016[62]). ZIN has conducted reviews of conditionally reimbursed technologies, which rely heavily on RWE generated throughout the period of conditional reimbursement (Makady et al., 2017[63]; Makady, 2017[64]).

The United Kingdom

116. The National Institute for Health and Care Excellence (NICE), which assesses the effectiveness and cost-effectiveness of technologies for the National Health Service (NHS) in England, considers all categories of evidence and requires that all available evidence be assembled systematically. NICE assessments are used, among other purposes, to inform reimbursement decisions by NHS payers, but generally not for pricing (van Nooten and Caro, 2013[54]). NICE assessments give greater weight to studies that employ methods to minimise potential bias, in particular RCTs (NICE, 2013[65]). However, NICE also recognises the limitations of evidence hierarchies and states that their use should not lead to the exclusion of valid non-RCT evidence from decision-making (Makady et al., 2017[63]). In 2015, 36% of single-technology assessments considered evidence from studies other than RCTs (Griffiths and Vadlamudi, 2016[59]). Methodological guidance published by NICE does not specify the sources of routinely collected data or the study designs to be applied to routinely collected data in order for such evidence to be considered "high quality."

117. Routinely collected data used in HTAs of medicines are mostly supporting data, rarely central to the decision-making process. However, the extent to which routinely collected data and evidence from clinical practice are used in HTA and the appraisal of medicines and treatments may change in the future, particularly given the advent of managed access agreements for certain treatments, e.g. highly specialised technologies for rare diseases and treatments recommended for use in the Cancer Drugs Fund.

118. A managed access agreement allows further data collection so that NICE's guidance can be reviewed when the clinical picture is clearer, and the additional evidence taken into account. Highly Specialised Technologies are treatments for ultra-rare conditions where it may not be possible to conduct RCTs, and where the natural history of the disease may be poorly understood, meaning that the full benefit of the treatment might not be fully captured in RCTs.

119. The new operating model of the Cancer Drugs Fund permits access to promising cancer treatments where there is significant clinical uncertainty. When NICE recommends a treatment for use in the Cancer Drugs Fund, there is managed access while further data are collected and the guidance is subsequently reviewed. The additional data may come from a clinical trial or other sources such as Public Health England's datasets. Outcome data for time on treatment and overall survival are captured using Public Health England's Systemic Anti-Cancer Therapy (SACT) data set.

United States

120. Several agencies perform health technology assessments in the United States, among them the Agency for Health Care Research & Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI).

121. Methodological guidance by the AHRQ, which conducts research on the effectiveness of health care interventions, defines the goal of comparative effectiveness research as to compare the benefits and harms of interventions in real-world settings. AHRQ's guidance on comparative effectiveness reviews states that evidence from both randomised and non-randomised studies should be considered and that the risk of bias in all types of studies, regardless of how data are obtained, should be evaluated (AHRQ, 2014[66]). The guidance further notes that data from administrative databases containing information routinely collected from health care encounters without specific research purpose should be used for reporting adverse events, but may be subject to issues of data quality and may thus be most useful for evaluating serious harms that are more reliably reported and recorded (ibid).

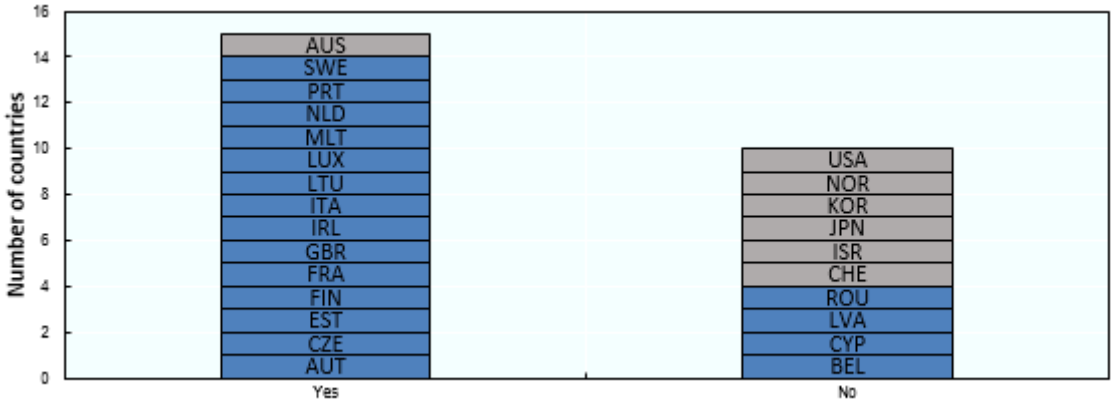
122. The Patient-Centered Outcomes Research Institute (PCORI) was created to promote the development and adoption of comparative effectiveness research (CER). PCORI conducts and funds studies of the comparative effectiveness of health care interventions, including technologies, in a similar manner to public HTA agencies in other OECD countries. A key limitation of federal CER and other similar initiatives related to effectiveness in the United States to-date is the lack of direct mechanisms to use this evidence to revise reimbursement conditions by public payers or prices. PCORI does not engage in cost-effectiveness research (111th U.S. Congress, 2010[67])Methodological guidance by PCORI does not provide a hierarchy of evidence (Hickam et al., 2013[68]). Guidance on studies using routinely collected data, in particular registries and databases of routinely collected data such as EHRs or insurance claims (referred to as "data networks"), focuses mainly on data quality and governance (ibid).

4.3. The extent to which reimbursement and pricing decisions rely on evidence from routinely collected data is unknown

123. Little information is available on the extent to which decision-makers and payers include evidence from clinical practice in price-setting and reimbursement decisions. In countries where pricing is based or negotiated on a measure of relative effectiveness, this may be related to the reliance of payers on assessments produced by national HTA agencies. The use of routinely collected data by payers themselves may be more limited, for example to model the budget impact of new technologies or to enforce price-volume agreements.

124. The 2018 OECD Survey on routinely collected data provided some insights into how countries potentially use routine data and evidence from clinical practice to guide decisions on reimbursement and price setting. More than half the responding countries have considered routinely collected data and evidence from clinical practice in price setting and reimbursement coverage decisions (Figure 4.4). As for the HTA processes, guidelines in many countries specify that all available research must be considered during the assessments, even though evidence from RCTs is given more weight. In Austria and Malta, for example, routinely collected data and evidence from clinical practice inform reimbursement decisions and inclusion in the list of publicly covered medicines. Likewise, in Italy routine data are included in reassessments of price and reimbursement, while Lithuania is currently revising reimbursement conditions for antibiotics in order to promote and facilitate responsible prescribing behaviour. Further details on country examples are provided below.

Figure 4.4. Countries reporting that routinely collected data can potentially be considered to inform price-setting or reimbursement decisions



Note: Missing information: Slovenia Blue colour indicates EU Member States, grey colour indicates non-EU OECD member countries.
Source: 2018 OECD survey on routinely collected data

Australia

125. The Australian Government funds medicines dispensed in the community through the Pharmaceutical Benefits Scheme (PBS), facilitating access to most prescribed medicines by subsidising their costs. The PBS is a universal coverage programme, which aims to provide all Australian residents and eligible foreign visitors with "timely, reliable, and affordable access to necessary medications".

126. Following marketing authorisation by the Australian regulatory agency (the Therapeutic Goods Administration), decisions on whether to make a product available for public subsidy, are made by the Minister for Health on the advice of the Pharmaceutical Benefits Advisory Committee (PBAC).

127. The PBAC is an independent statutory body that recommends pharmaceuticals and medicinal preparations to the Minister for funding under the PBS, and since 2006 recommends vaccines for funding under the National Immunization Program (NIP). The PBAC guidelines, which were developed to guide sponsors to prepare consistent and comprehensive submissions, specify the clinical and economic data that must be presented. PBAC has a strong preference for clinical and economic evaluations that are based on randomised controlled trials but recognises that these are not always available.

128. The criteria applied by the PBAC to determine whether to recommend a pharmaceutical for listing on the PBS include: the comparative health gain (effectiveness, safety); comparative cost-effectiveness; the financial implications for PBS and government health budgets; the severity of the condition treated; the presence of effective alternatives; the ability to target therapy to those most likely to benefit; uncertainty around the clinical evidence, cost-effectiveness and projected budget impact; the affordability of the medicine in the absence of a subsidy; issues of equity; and the "Rule of Rescue". The criteria are subject to qualitative judgments and deliberation; these criteria are not weighted equally and some factors may be more or less important in different situations. In making its recommendations, the PBAC, on the basis of community usage, recommends maximum quantities and repeats of medicines and may also recommend restrictions to current indications where PBS subsidy is available. The Department of Health may sometimes negotiate the prices of the proposed medicines with the suppliers and any special arrangements such as risk sharing or managed entry agreements.

129. Post-market Reviews (PMR)[13] were introduced in 2012 to ensure the ongoing sustainability of the PBS by ensuring the continued safe, effective and cost-effective use of PBS-listed medicines. The Department of Health uses both RCTs and evidence from clinical practice when conducting PMRs of medicines listed on the PBS. Routinely collected data on medicine dispensing and prescriber data have been used to determine if PBS listed medicines are used appropriately for those indications and populations in which they were previously assessed as being cost-effective. These data sources include the Medicare Australia PBS dataset, as well as a dataset known as MedicineInsight[14]. Longer-

[13] Information and PBS Post-market Review Reports are available at: http://www.pbs.gov.au/info/browse/reviews.

[14] MedicinesInsight is a quality improvement programme developed and managed by NPS MedicineWise with funding from the Australian Government Department of Health. The programme uses a novel model, which collects routine clinical data from GPs' clinical software, including prescribing data (NPS MedicineWise, 2018[111]).

term observational studies are also considered in post market reviews to inform PBAC on the safety of medicines when used in the broader population post registration and subsidy.

130. Some examples of the use of routinely collected data to inform these policies include:

- In 2003, the PBAC recommended the listing of ezetimibe on the PBS based on a comparison of data on lipid levels. In 2013, the PBAC expressed concern that the listing of ezetimibe with statin co-packs and combination products on the PBS may have directed patients away from optimal dosing with a statin first. The PBAC also noted that, in contrast to statins, there was still no data on patient relevant outcomes for ezetimibe, and that PBS expenditure on ezetimibe was high. In 2015, the PBAC recommended a review of the cost-effectiveness of ezetimibe, to reflect the latest available evidence and best clinical practice. The Post-Market Review (PMR) Report submitted to the PBAC collated all available evidence, including evidence from clinical practice obtained through a medicine utilisation analysis of PBS dispensing data. The evidence from clinical practice identified the extent to which that ezetimibe was being prescribed to patients who had not been trialled or optimally titrated on a statin before commencing ezetimibe. There was no evidence to support the cost-effectiveness of ezetimibe used in this way, i.e. in preference to statins. On considering the ezetimibe PMR Report, the PBAC recommended a price reduction of ezetimibe to restore its cost-effectiveness ; and a change in PBS restrictions to reinforce to prescribers that use of ezetimibe should be limited to patients with high cardiovascular risk following optimal titration of statin therapy (see Annex 2 for further details).
- In another case, a review of the utilisation of novel oral anticoagulants (NOACs) used in the prevention of stroke or systemic embolism in non-valvular atrial fibrillation (NVAF) led to the establishment of risk-sharing agreements with an expenditure cap for companies. The Drug Utilisation Sub-Committee (DUSC) of PBAC reviewed the predicted versus actual use and, based on the volume of prescriptions, it found that NOACs had contributed to an overall growth in the anticoagulant market since their listing on the PBS for NVAF, in spite of a decline in the use of warfarin. The three NOACs were listed in August and September 2013. Shortly after the listing, the TGA issued a safety advisory for these medications based on evidence from international post-marketing surveillance. To manage the total costs of this therapeutic area to the PBS, the PBAC advised that the listing should be subject to a "risk-sharing arrangement" between the sponsor and the government with 100% of expenditure above the agreed estimates to be rebated to the government.

Estonia

131. The Medicines Department, established within the Ministry of Social Affairs in 2002, is responsible for strategic planning regarding pharmaceuticals, as well as for pricing and reimbursement decisions. Since 2018, the Estonian Health Insurance Fund (EHIF) has taken over responsibility for administering the positive list and price setting. The State Medicine Agency and the EHIF advise the Ministry of Social Affairs on reimbursement (Habicht et al., 2018[69]). In this process, evidence from clinical practice is included in cost-effectiveness assessments and budget impact analysis.

Finland

132. While evidence derived from RCTs is most frequently used to inform price setting and reimbursement decisions, analyses sometimes take into account routinely collected data from the Finnish Prescription Registry. For instance, Finland introduced generic substitution in 2003 and reference-based pricing in 2009. The impact of these to policy measures on the prices of antipsychotics in Finland was assessed, using data on reimbursed prescriptions dispensed in pharmacies. The study identified potential weaknesses in the Finnish reference pricing system. All reimbursed medicines have a maximum wholesale price at which wholesalers can sell products to pharmacies. Authorities do not review maximum prices for products included in the reference pricing system. This means that though price competition in most cases reduces actual prices and reference prices to below the confirmed maximum wholesale prices, market authorisation holders operating in submarkets with low competition always have an opportunity to raise their prices to match the maximum wholesale prices. This was observed for two of the antipsychotics included in the study, for which market authorisation holders simultaneously raised their prices to match the confirmed wholesale price of the generic product (Koskinen et al., 2015[70]). In an attempt to tackle increasing reference prices, the calculation of reference prices changed in 2017 (see Annex 2 for further details).

France

133. There is no systematic use of evidence from clinical practice in reimbursement and pricing processes. In France, after marketing authorisation all medicines–except generics—must be assessed by the Transparency Commission of the High Authority on Health. The Transparency Commission determines the absolute and relative (by comparison to existing treatments) therapeutic value of new medicines. The absolute therapeutic value is used to determine reimbursement conditions while the relative value is used to determine or negotiate the price with the manufacturer.

134. In the majority of cases, the Transparency Commission re-assesses the medicine every five years, and ad-hoc re-assessment may be triggered by new evidence of the safety or efficacy of specific products or classes of products. Assessment reports sometimes refer to studies based on evidence from clinical practice ("études observationnelles"), to complement evidence drawn from RCTs and meta-analyses. In addition, where there is a lot of uncertainty in the evaluation of efficacy when the drug is assessed for the first time, the Transparency Commission may require a prospective study to be performed within a given timeframe for re-assessment. The company is required to provide these data and the study is designed with the HAS' endorsement of outcomes. These studies however, do not rely on routinely collected data.

135. In a few cases, evidence from clinical practice has led to a product delisting following a re-assessment of the risk-benefit balance. For example:

- Following the publication of a study showing an increased risk of enteropathy in patients treated with olmesartan, the French Medicines Agency (ANSM) enhanced its monitoring of patients receiving medicines containing angiotensin II receptor antagonists (A2RAs). Based on data from the French reimbursement claims (SNIIRAM) and hospital discharge (PMSI) databases, the analyses showed that patients treated with olmesartan were at higher risk of developing enteropathy, which patients treated with other types of A2RAs were not. As a result, products containing olmesartan were delisted from the reimbursement formulary in January 2017.

- Similarly, routinely collected data from SNIIRAM and PMSI were used in a risk assessment of combined hormonal contraceptives. The analyses identified that women receiving 3rd generation combined hormonal contraceptives (CHC) were at elevated risk of developing ischemic stroke, pulmonary embolism and myocardial infarction. From March 2013, 3rd generation CHCs were no longer reimbursed in France (see Annex 2 for further details).

136. The Pricing Committee (CEPS) negotiates the prices of all new drugs with individual companies at launch and then regularly. The committee is in charge of the regulation of pharmaceutical spending through macro-economic and product specific agreements. The Committee does not use health insurance data to define rebates to be paid by companies partly for timing reasons. Instead, the Committee uses sales data produced by the private company GERS on a monthly basis, to compute volumes and sales and determine rebates where relevant.

Israel

137. Publicly-funded health care in Israel is provided by four not-for-profit health plans, which receive tax-funded budgets from the Ministry of Health. As integrated provider and payer organisations, health plans make extensive use of their own routinely collected data, not only for individual treatment but also broader policy decisions (Rosen, Waitzberg and Merkur, 2015[71]). Statutory reimbursement coverage of new services and technologies is determined annually for all insurers by the government and the Ministry of Health, based on recommendations made by a public committee. The decisions are informed by analyses that rely on routinely collected data from the health plans, but only to identify target populations and estimate the dissemination and budget impact of potential new additions (personal communication).

The United States (Department of Veterans Affairs, VA)

138. The US Department of Veterans Affairs, which provides health coverage to retired military and their families, has one of the most comprehensive administrative datasets available in the United States. This has permitted the conduct of research using real world databases to help determine the root cause of safety signals associated with drugs, as well as to close the gap between efficacy and effectiveness. It has amassed a number of real-world data sets, including the National Drug Evaluation Network, the National Veterans Affairs System, the Target Cities studies, the state data systems in Michigan and Washington, and the Community Epidemiology Laboratory.

139. The VA conducted a retrospective cohort study at the request of the FDA to evaluate the incidence of mental health hospitalisations among veterans using various smoking cessation medications. The study's main outcome was psychiatric hospitalisation 30 days after a prescription fill. There were 16 psychiatric hospitalisations among 14 131 patients treated with varenicline, and 21 hospitalisations among an equal number of nicotine replacement therapy (NRT) users. The study found no statistically significant difference in the risk of psychiatric hospitalization for varenicline users compared to NRT users (hazard ratio for varenicline /NRT = 0.76; 95% CI 0.40-1.46). Despite this inconclusive evidence, the FDA cited study limitations in its subsequent decision to publish a Drug Safety Communication for varenicline (FDA, 2011[72]).

140. Another therapeutic area that has been the subject of much scrutiny in the VA system has been the new generation of anticoagulant therapies. VA data have been extensively reviewed to examine anticoagulant outcomes ((Rose et al., 2011[73]); (Nelson

et al., 2015[74]) (Rose et al., 2016[75])), adverse events ((Abraham et al., 2013[76]), (Jasuja et al., 2013[77])), adherence ((Shore et al., 2014[78])), quality measurement ((Razouki et al., 2015[79])) and cost (Rose et al., 2011[80])). However, a direct link tying this information to reimbursement decision-making was not immediately apparent.

141. At present, the VA maintains a hepatitis C registry containing every VA patient diagnosed with HCV. Among the information collected is genotype, viral load, prior treatment, progression to advanced liver disease, treatment response, adverse events, and discontinuation. There are weekly reports for new prescriptions of each available HCV medication at the national, regional, and site facility level. This information is used to give benchmarking feedback to facilities on drug choice, as well as for comparative effectiveness research and contracting purposes (Good, 2016[81]).

4.4. Routinely collected data can have an indirect effect on utilisation by informing practice guidelines

142. Research studies can have a direct or indirect impact on consumption. Studies detecting either over- or underuse of medicines, or inappropriate prescribing, may point towards poor compliance with guidelines or poorly developed guidelines. In order to improve and ensure good quality of care to patients, clinical practice guidelines may be revised, as demonstrated by the following examples from Australia, Finland, France, Israel and the United Kingdom.

Australia

143. The number of patients treated for attention deficit hyperactivity disorder (ADHD) and associated PBS expenditure have grown steadily in recent years. The Australian Drug Utilisation Sub Committee (DUSC) reviewed the utilisation of PBS-listed medicines used in the treatment and management of ADHD, using prescription claims data. The review provided several valuable insights. Prescription rates varied significantly across the states and territories. While adults still represented a slightly higher proportion of people treated over time, they did not constitute a higher proportion of patients new to treatment. Of particular concern was the prescription of antipsychotics issued to children aged 5 years and younger. As a result, the DUSC review was submitted to the National Prescribing Service in order to support the quality of use and prescription of medicines used in the treatment of attention deficit hyperactivity disorder (ADHD) (see Annex 2 for further details)

Finland

144. The Finnish Prescription Registry often informs research that potentially further impacts clinical practice and prescription patterns. In 2011, researchers conducted a register-based, national study to detect potentially inappropriate medication use among the non-institutionalised elderly population and quantify the total annual reimbursement costs in Finland. The cohort counted 123 545 people who had received potentially inappropriate medicines with a corresponding reimbursement cost to the Social Health Insurance Institution equivalent to €2.9 million (0.7% of total reimbursement costs in Finland). While the potentially inappropriate use of medicines was low by comparison to other countries and reimbursement costs were modest, benzodiazepines were frequently prescribed to patients aged 65 or more, and thus actions targeting medication safety should aim to reduce their use (see Annex 2 for further details). This and several other studies have indicated the

problematic medicine use especially in the elderly in Finland. Long-term use of benzodiazepines has started to decrease since 2008.

France

145. In 2013, a study conducted with the SNIIR-AM and including 163,801 patients showed no superiority of rosuvastatin over simvastatin in the primary prevention of, and mortality due to stroke and myocardial infarction. (Neumann et al., 2013[82]) Such a study could justify a revision of guidelines to recommend treatment initiation with simvastatin rather than rosuvastatin, since the former (already off patent) is cheaper than the latter (see Annex 2 for further details). The impact of this guideline revision is unknown.

Ireland

146. In 2013, the Irish Health Service Executive (HES) established the multidisciplinary Medicines Management Programmes. The MMP works alongside the National Medicines Information Center in collaboration with the HSE-Primary Care Reimbursement Service (HSE-PCRS) to provide sustained national leadership in the management of medicines and expenditure. The MMP has undertaken several initiatives targeting evidence-based and cost-effective prescribing by providers. One of these initiatives is the Preferred Drugs Initiative, for which routinely collected data were included in the analyses and informed the recommendations guiding prescribers towards prescribing the antidepressants of proven safety, efficacy and cost-effectiveness in the management of patients with depression. However, the effect these recommendations have had on prescription patterns and medicine use remains unknown.

Israel

147. Based on routinely collected data from the Clalit database, researchers assessed statin use in the prevention of cardiac events in patients with ischemic heart disease. Although international guidelines recommend preventive treatment of patients with a history of ischaemic heart disease, they differ in terms of target levels of low-density lipoprotein. The Clalit cohort covered about 86 000 patients requiring secondary prevention. Based on the results of this study, Clalit refrained from lowering treatment targets (see Annex 2 for further details).

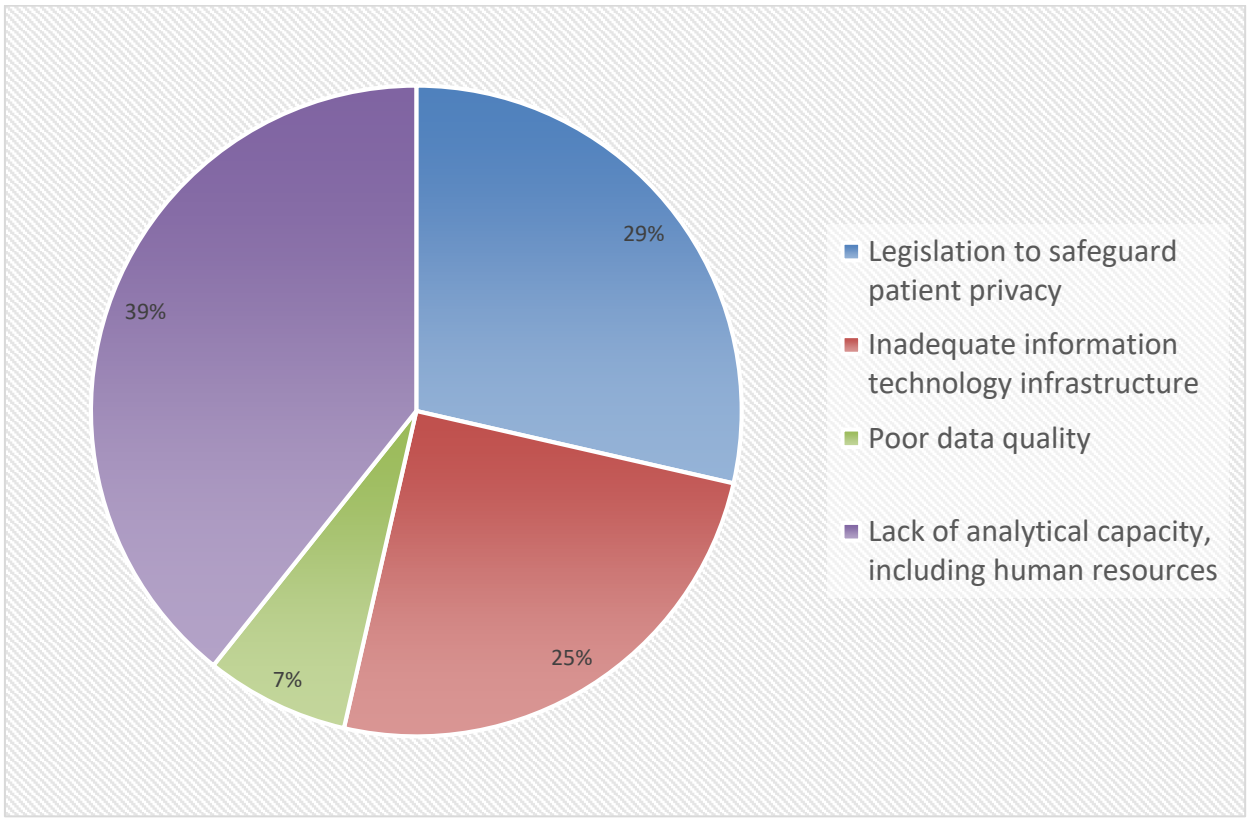
United Kingdom

148. Routinely collected data extracted from the CPRD database have been used to monitor and support a vaccination programme targeting pregnant women in the United Kingdom. A peak in the incidence of pertussis (whooping cough) and a number of deaths in infants too young to be vaccinated led to the introduction of a temporary vaccination program targeting women in their third trimester of pregnancy. The vaccine had not been used extensively in pregnancy, and the product information advised against it. Proactive monitoring of the safety and effectiveness of the programme was thus initiated. A cohort of 20 000 pregnant women were identified via routinely collected data and matched with an unvaccinated cohort. The results of the proactive and continuous monitoring and surveillance of the vaccine have supported the continuation of the vaccination program (see Annex 2 for more details).

4.5. Barriers to increased use of evidence from clinical practice

149. The majority of responding countries recognise the under-exploited potential of routinely collected data and evidence from clinical practice. When asked to identify the key barriers to increased use and application of evidence from clinical practice, the responding countries pinpointed three core barriers: lack of analytical capacity (39% of respondents); the legislation to safeguard patient privacy (29%); and inadequate information infrastructure (25%) (Figure 4.5). Interestingly, only 7% of the responses listed poor data quality as the main barrier to using routinely collected data or evidence from clinical practice in their daily decision-making processes. These results indicate where countries could make efforts to increase the use of evidence from clinical practice.

Figure 4.5. Lack of analytical capacities is most common barrier reported by countries (% of all responses mentioned as common barriers by the 26 respondents)



Note: Countries could indicate several barriers.
Source: 2018 OECD survey on routinely collected data

5. Conclusions and recommendations for use of routinely-collected data

150. A consensus is emerging on promoting the concept of a learning health system, one able to draw on the rich information it generates to drive both enhanced outcomes for patients and better economic performance, including in the pharmaceutical domain (Eichler et al., 2018[7]). Through a country survey and desk research, this study explored the availability, accessibility and use of routinely collected data to manage medicines (regulation of market entry, coverage and pricing, practice guidelines) in OECD and EU countries. It confirms that countries are unevenly prepared both in terms of data infrastructure and governance to fully leverage routinely collected data to improve pharmaceutical care.

151. Patient-level data on medicines collected in routine most often come from pharmacy records, electronic health records or insurance claims. They rarely cover medicines dispensed in hospital, which is an important gap. Responding countries reported that they primarily use routinely collected data on medicines to monitor consumption and spending levels (22/26 countries), provider compliance with guidelines (18 countries), prescribing quality and behaviour (15 countries), and to evaluate safety and inform changes in clinical practice (14 countries). Routinely collected data were used less frequently to perform comparative effectiveness evaluations or cost-effectiveness studies.

152. The responses to the survey, illustrated by concrete examples, do not allow for an evaluation of the *extent* to which this information is used in the management of medicines. Even in countries where evidence drawn from these databases has been used in hundreds of scientific publications, it was not possible to determine, within the scope of this project, how often these studies—or other non-published studies—have been used as a basis for revising indications, clinical practice guidelines, coverage conditions, or prices. The majority of countries (19), however, reported that routinely collected data were not "used to their full potential" in their healthcare systems. The main barriers identified were a lack of analytical capacity; the legislation to safeguard patient privacy; and inadequate information infrastructure.

153. The following sections suggest a roadmap for progress towards using these data to enhance the performance of health systems, and more specifically, to improve pharmaceutical care.

5.1. Further development of methods may increase the leverage of routinely collected data in medicines management

154. While methods for studies of drug safety and drug utilisation based on clinical trials are now very well established, methods for the use of routinely collected data for studying effectiveness are less well developed. Most policies and methodological guidance documents made available by regulatory and HTA agencies and reviewed for this report recognise that routinely collected data can be a legitimate source of evidence with respect to its external validity and generalisability. The notable exception to this is the German IQWiG, which maintains that only evidence from RCTs should inform health technology assessments. The extent to which evidence from clinical practice is considered by such agencies, however, varies significantly. Most policy documents, including guidance by IQWiG, also recognise that evidence hierarchies based on study designs are a blunt tool and fail to provide a nuanced understanding of the validity of findings in addressing

research questions at hand. Nevertheless, evidence hierarchies continue to be maintained and evidence derived from routine data is generally considered to be of lower quality and given less weight by HTA agencies. A number of practical and cultural barriers to wider use of RWE remain (Makady, Goettsch and Willemsen, 2015[36]).

155. Contrary to guidance for conducting RCTs, guidelines on evidence from clinical practice remain relatively vague on requirements for data sources, study designs and methods, leaving significant leeway to study sponsors and investigators. This is likely associated with the relative novelty of sources of routinely collected data and appropriate methods for their analysis, as well as the current lack of universally accepted definitions. A recent stakeholder meeting in the United Kingdom called for greater clarity in the requirements of HTA agencies and regulators, in order to realise the potential of routinely collected data (ABPI, NICE and University of Manchester, 2016[83]). There is already a relatively large and growing body of literature on study designs and analytical methods that allow for addressing some of the main issues associated with observational studies, such as bias and confounding, which could be used in making guidance more specific. Laying out general requirements on acceptable data sources, however, may be significantly more difficult because, by definition, routine data are not collected for research purposes. Although there are mechanisms to improve the quality and consistency of data, such as defining minimum datasets, requiring the use of standard coding systems and definitions and auditing adherence to such regulations (OECD, 2013[14]), data collected in routine practice are likely to remain less reliable for research than data collected in prospective studies using strict protocols.

156. Recent initiatives from the European Commission support research on the development of methodological approaches to collect, integrate and analyse routinely collected data. Some of these initiatives, IMPACT HTA and HTx for example, focus on the application of evidence from clinical practice in economic evaluations. Other initiatives, such as PECUNIA, address specific research needs when it comes using patient-preferences and evidence from clinical practice in evaluating costs, outcomes for medical devices and developing standardised, harmonised and validated methods for the assessment of healthcare interventions targeting chronic and mental health care.

5.2. Improved data infrastructure and data governance are key elements of learning health care systems

157. OECD and EU countries currently have very uneven capacities to harness routinely collected data to improve pharmaceutical care, but many could make progress in terms of data infrastructure and governance. The OECD Council has already put forward a number of recommendations on health data governance, which are valid in this context (OECD, 2017[18]). This report, like previous OECD reports (OECD, 2013[14]; Oderkirk, 2017[9])), also enables countries to benchmark themselves against other countries and "best practices". Countries' relative positions in terms of capacity to harness routine data for medicines management are not entirely different from their positions in terms of preparedness to harness health data from EHR for research (Oderkirk, 2017[9]). The only difference is that the 2018 survey considered a wider set of routinely collected data, including insurance claims, and showed that the latter can be harnessed to conduct pharmaco-epidemiologic studies of interest for regulators, HTA agencies and policy makers.

158. A key barrier to the wider use of routinely collected data is that they often do not contain measures of outcomes that are sufficiently accurate and complete to estimate

effectiveness or cost-effectiveness of health interventions. In this respect, EHR data may be better suited than databases generated from reimbursement claims, since they often include information that can be considered surrogate outcomes. The development of Patient Reported Outcome Measures (PROMs) and inclusion in routine datasets may enhance the utility of routine data in optimising pharmaceutical care or conducting comparative effectiveness research.

159. This report does not address the role of the industry in the production of evidence derived from routinely collected data. A 2013 study by IMS suggested that the uptake of real-word data (in the broader sense, not limited to routinely collected data) was uneven across countries and across companies (IMS Health, 2013[84]). This study also showed, from a sample of about 100, that many studies performed or sponsored by the industry were intended to inform managed entry agreements and guarantee "launch access", or to influence coverage conditions by demonstrating value and ensuring "ongoing access" (ibid). In the 2018 OECD survey, only a few countries reported that private companies may be granted access to routinely collected data. In addition, this access can be subject to conditions, such as a requirements that the study is in the "public interest" and that the results are shared with the authorities and/or the general public. This represents a risk companies might be reluctant to take. However, this risk has to be balanced with the risk of ceding the initiative to public authorities, which might be led by circumstances and their own priorities, to focus on studies responding to safety alerts, suspicion of misuse and overuse, and with a high probability to show "negative" results. These studies are crucial to promote an appropriate and efficient use of medicines but the ideal "learning system" goes beyond that, and should also aim to demonstrate the value of medicines in clinical practice.

5.3. Cross-border knowledge-sharing could also be improved

160. Another objective of this report was to explore how knowledge generated from routinely collected data is shared among countries. On this aspect, the evidence is weak. While new knowledge on the safety of medicines is shared, at least at EU level through EMA's activities, there is no evidence that other types of knowledge generated at country level are used by other countries.

161. Scientific publications indexed in bibliographic databases used in pharmaco-epidemiology (e.g. Medline) might be considered by HTA agencies undertaking re-assessment of existing technologies. Studies conducted at the national level, however, may not be indexed in such databases and may only be available in a national language. In these circumstances, studies based on routine data are less likely to be known and used by other countries. Although some of them may not be generalisable to other contexts (e.g. studies monitoring use), others might provide useful information on specific products for decision-makers.

162. The creation and use of a common repository, including a full list of studies derived from routinely collected data, as well as tools to search for information by product or class, would require considerable investment from a wide range of stakeholders across countries. The extent to which the costs and efforts of building up a repository would be worth the benefit remains unclear. However, better promotion of national research based on routinely collected data and cross-border knowledge sharing would appear to be worthwhile.

163. One option to increase knowledge sharing across borders would be to increase the number of indexed publications derived from these studies. This objective could be reached

by facilitating access to data for researchers, or by providing non-academic institutions producing these studies (e.g. health insurance funds) with incentives to get them published in peer-reviewed journals. A publication in a peer-reviewed journal increases the diffusion of results—especially if the publication is in open access—and assures a certain level of methodological rigour. Getting scientific papers published is a long and costly process, which might require training and support for the staff in these institutions. Such efforts, in a context of stretched resources and lack of capacity reported by countries, would need to focus on new knowledge which is particularly relevant, transferable to other contexts or generalisable, and actionable; i.e. likely to influence clinical practice for better outcomes.

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Annex 1 - Survey on routinely collected data on pharmaceutical prescription/dispensing

Please provide the contact information of the person primarily responsible for the completion of this questionnaire.

Country
Name
Position
Organisation
Email
Telephone

1) Are patient-level data on prescribed and/or dispensed medicines *routinely* collected in your health care system?

Note: patient-level data refers to patient-level de-indentified prescribing or dispensing data that are not only collected in aggregate.

○ Yes (please also answer questions 1.a., b., c., d., e., f., g. below)
○ No (please describe briefly the reasons why in h.)

If yes,

a) What type of patient-level data is collected (please select all that apply):

○ Information on medicines reimbursed by health coverage schemes (public or private)
○ Information on medicines prescribed by physicians
○ Information on medicines dispensed by pharmacists
○ Information on medicines dispensed in hospitals
○ Information on medicines dispensed in ambulatory care clinics and long-term care institutions
○ Other, please specify

If other, please specify

b) What sources are these data extracted from? (please select all that apply)

○ Personal health records (completed by physicians or other health care professionals working in general practice, ambulatory care clinics or hospitals)
○ Community pharmacy records (completed by pharmacists or ePrescriptions)
○ Insurance claims data, including payment data for single-payer systems
○ Other, please specify

If other, please specify

c) Are these data aggregated at the national level?

○ Yes, these data are collected at the national level and made available in a database at the national level
○ Yes, these data are collected at the regional/health insurance level then aggregated and made available in a database at the national level
○ No, these data are only available in separate databases at the regional/health insurance level (please explain the reasons for why these data are not aggregated below and answer to Q1d., e., f., g.)
○ Other, please specify

If other, please specify

d) What proportion of the national population is covered by these data?

○ The whole population
○ Only a fraction of the population, please specify the share of population covered XX %

Please comment

e) Over what time period have patient-level data on prescribed/dispensed medicines been available in your database(s)?

Please indicate since when such data are available (year):

Start year	
Latest year available	

f) What is the policy regarding the storage of these data?

○All data collected are kept indefinitely and possible to access
○ A cohort of data (or only a section of these data) is kept indefinitely
○ Data are kept and stored for a defined period of time only after a period of time (please indicate)
X months/vears
○ Other, please specify

If other, please specify

g) Please provide the name(s) or acronym(s) of the database(s) where these data are held, and the name of the authority that is the custodian of these data (specify by sector if available):

Note: The "custodian" is the institution primarily responsible for data management, security and access

Please specify

h) If you responded "no" to Q1, please briefly explain the reasons for why such data are not collected

Please comment

2) Do these data also include other types of patient-level information beyond prescriptions/dispensing of medicines?

○Yes
○ No

a) Please select all that apply:

○ Demographic characteristics of patients (e.g. age, gender)
○ Physiologic characteristics of patients (e.g. height, weight)
○ Diagnoses associated with every pharmaceutical prescription
○ Other diagnoses not associated with prescriptions
○ Patients' medical history
○ Results of laboratory tests
○ Results of medical imaging
○ Outcomes of treatment (including adverse events)
○ Mortality
○ Other measures of health status (e.g. physical functioning, quality of life, etc. – please specify below)
○ Life-style (e.g. smoking status)
○ Utilisation of social care services

○ Utilisation of other healthcare services, please specify

Patients' utilisation of other types of healthcare services, such as doctors' consultations, hospitalisations, laboratory tests, medical imaging, prescribed/implanted medical devices etc.

○ Other, please specify

If other, please specify

b) Can the medicine/dispensing database be linked to other databases containing patient-level information by for example using a unique person identifier or probabilistic data linkage?

Record linkage involves linking two or more datasets using information that identifies the same patient or the same person. An example would be linking patient records in a hospital database to any death records of the same persons in a mortality database in order to identify patients who died following treatment.

○ Yes (please also answer c and d)
○ No

c) If yes, what sort of information can these data potentially be linked to? Please select all that apply.

○ Demographic characteristics of patients (e.g. age, gender)
○ Physiologic characteristics (e.g. height, weight)
○ Diagnoses associated with every pharmaceutical prescription
○ Other diagnoses not associated with prescriptions
○ Patients' medical history
○ Other information extracted from disease-specific registries
○ Results of laboratory tests
○ Results of medical imaging
○ Genetic information
○ Mortality
○ Other measures of health status (e.g. physical functioning, quality of life, etc. – please specify below)
○ Life-style (e.g. smoking status),
○ Environnemental information (e.g. air pollution)
○ Utilisation of social care services
○ Utilisation of other healthcare services, please specify

Patients' utilisation of other types of healthcare services, such as doctors' consultations, hospitalisations, laboratory tests, medical imaging, prescribed/implanted medical devices etc.

○ Other, please specify

If other, please specify

d) Please provide name and contact details of a person knowledgeable about the content of the database(s) and, if any, record linkage practices.

Name:
Organisation:
Position:
Email address:
Telephone :

3) Other than the employees of the data custodian, can other individuals/organisations be approved access to the database for the purpose of secondary use (e.g. for the purpose of quality and performance monitoring, research, safety of medicines etc…)?

Note: The "custodian" is the institution primarily responsible for data management, security and access

○ Yes (please answer a)
○ No

a) Who can get access to data for the purpose of secondary use? (please select all that apply)

○ The Ministry of Health or other governmental ministries in your country
○ The medicine regulatory agency
○ Health care payers (e.g. compulsory health insurance funds, regional authorities, etc.)
○ Non-profit research units and/or universities (academics)
○ Other stakeholders (consultants, pharmaceutical companies, voluntary health insurers, etc…)

If other, please specify

4) Have data on medicine prescriptions/dispensing already been used to (please select all that apply):

○ Monitor trends in medicines consumption and/or spending at national level
○ Inform/change clinical practice
○ Monitor patient adherence to treatment
○ Monitor provider compliance with guidelines
○ Monitor prescribing quality and behaviour
○ Evaluate the safety of medicines
○ Evaluate the effectiveness of medicines
○ Evaluate the comparative effectiveness of medicines
○ Evaluate the cost-effectiveness of medicines
○ Other, please specify

If other, please specify

a) If you selected at least one of the answers to question Q4, please provide 1 to 3 specific examples of how data or study results were used. Please find examples below.

Example 1: Assessment of statin use in prevention of cardiac events in patients with ischemic heart disease in Israel, based on data routinely collected by Clalit

Study	*Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment (Leibowitz et al. 2016)*
Objective	*To assess the association between levels of low-density lipoprotein cholesterol (LDL-C) achieved with statin treatment and cardiovascular events in adherent patients with pre-existing ischemic heart disease.*
Motivation	*International guidelines recommend treatment with statins for patients with pre-existing ischemic heart disease to prevent additional cardiovascular events, but differ regarding target levels of low-density lipoprotein cholesterol (LDL-C). Trial data on this question are inconclusive. Nevertheless, there has been a push to reduce LDL-C treatment targets in secondary prevention of cardiovascular disease to 70 mg/dL for all patients.*
Data	*Data for all Clalit Health Services members from the Clalit data warehouse. Anonymous patient data were compiled from EHR, the Clalit chronic disease registry, hospital discharge summaries, and pharmacy and laboratory records. Demographic data were obtained from the Israeli Central Bureau of Statistics and the Ministry of Internal Affairs. The final study population comprised 31,619 patients who were at least 80% adherent to statin treatment and 54,884 patients who were at least 50% adherent. Estimates were made between non-matched treatment groups using a proportional hazards model adjusted for clinical and socio-demographic variables and between propensity-score matched treatment groups.*
Inclusion criteria	*Patients with ischemic heart disease and requiring secondary prevention, aged 30 to 84 years, treated with statins for at least one year before the first serum LDL-C value measured at any time between 2009 to 2013, and at least 80% adherent to treatment or, in a sensitivity analysis, at least 50% adherent. Patients with active cancer or metabolic abnormalities were excluded.*
Outcomes of interest	*Time to major adverse cardiac events (MACE), including acute myocardial infarction, unstable angina, stroke, angioplasty, bypass surgery, or all-cause death.*
Results	*Patients with LDL-C levels of 70 to 100 mg/dL taking statins had lower risk of adverse cardiac outcomes compared with those with LDL-C levels between 100 and 130 mg/dL, but no additional benefit was gained by achieving LDL-C of 70 mg/dL or less.* *Incidence of adverse outcomes, adjusted for socio-economic and clinical variables, was not different between low and moderate LDL-C (hazard ratio 1.02; 95% CI, 0.97 to 1.07) but was lower with moderate vs high LDL-C (hazard ratio 0.89; 95% CI 0.84 to 0.94). Among 54,884 patients with at least 50% statin adherence, the adjusted hazard ratio was 1.06; 95% CI, 1.02 to 1.10 in the low vs moderate groups and 0.87; 95% CI 0.84 to 0.91 in the moderate vs high groups.*
Policy impact	*Based on the result of this study, Clalit refrained from lowering treatment targets and maintains that achieving LDL-C levels below a threshold of 100 mg/dL is sufficient. National news channels and papers have covered results of this study extensively and impact on policy was still unfolding at the time of writing of this report (personal communication with Prof Ran Balicer, Director of the Clalit Research Institute).*

Example 2: Assessment of the link between Benfluorex and valvular heart disease in France

Study	*Weill A. et al. (2010), Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus, Pharmacoepidemiology and drug safety; Vol. 19, pp. 1256–1262.*
Objective	*Assess the link between benfluorex and risk of valvular heart disease, motivated by safety alerts*
Motivation	*Safety alerts*
Data	*Health insurance claims (SNIIRAM) and hospital discharges (PMSI).*
Inclusion criteria	*All patients aged 40–69 years with reimbursement for oral antidiabetic and/or insulin in 2006 (1 048 173 patients).* *"Exposed Patients" were patients with at least one benfluorex reimbursement in 2006 (43 044 patients).*
Outcomes of interest	*Selected admission diagnoses of interest in 2007 and 2008 PMSI databases were valvular insufficiency for any cause, mitral insufficiency, aortic insufficiency, and valvular replacement surgery with cardiopulmonary bypass.* *Adjusted Relative risks (ARR) exposed/non-exposed were adjusted on gender, age, and history of chronic cardiovascular disease.*
Results	*Benfluorex in diabetic patients was significantly associated with hospitalization for valvular heart disease in the 2 years following benfluorex exposure.* *ARR of hospitalization in 2007 and 2008 for any cardiac valvular: 3.1 [2.4–4.0], with a lower risk for patients with lower cumulative dose of benfluorex. ARR for mitral insufficiency and aortic insufficiency admissions were 2.5 [1.9–3.7] and 4.4 [3.0–6.6], respectively. ARR for valvular replacement surgery was 3.9 [2.6–6.1].*
Policy impact	*Benfluorex (Mediator®) was withdrawn from the market on November 2009, one month after results were communicated for the drug agency.* *This case led to changes in the drug legislation because it took a lot of time for recurring alerts to be taken into account by regulators.*

b) Is there a repository where we can find a list of all studies performed with these data?

○ Yes (please indicate where it can be found)
○ No (please answer to c)

If yes, please indicate where the repository can be found

c) If there is no repository, can you provide examples of studies that used these data mentioned in Q4 to assess the effectiveness, cost-effectiveness or other measures of performance of medicines?

If yes, please indicate where the repository can be found

5) Do regulatory bodies in charge of issuing market approval in your country take such studies into account in their assessments and decision-making?

○ Yes (please provide examples below)

Please provide examples of where routinely collected data have influenced the decisions on market approval

○ May be taken into account, as analyses based on observational data are graded lower than evidence derived from randomised controlled trials
○ Regulatory bodies do not consider such evidence
○ There is no post-marketing assessment
○ Other, please specify:

If other, please specify

6) Do health technology assessment bodies in your country take such studies into account in their assessments and decision-making?

○ Yes (please provide examples below)

Please provide examples of where routinely collected data have influenced the outcome of health technology assessments

○ May be taken into account, as analyses based on observational data are graded lower than evidence derived from randomised controlled trials

○ Health technology assessment bodies do not consider such evidence

○ Other, please specify:

If other, please specify

7) Are such studies potentially considered to inform price-setting coverage decisions on inclusion in or exclusion from the package of publicly-funded medicines?

○ Yes (please explain below)

Please provide examples of where routinely collected data have influenced coverage decisions or price-setting

○ No

8) Do you believe that routinely collected data are used to their full potential in your healthcare system?

○ Yes
○ No (please answer a)

a) If **no**, can you please indicate the barriers to their use?

○ Legislation to safeguard patient privacy

○ Inadequate information technology infrastructure

○ Poor data quality

○ Lack of analytical capacity, including human resources

○ Other, please specify

If other, please specify

9) If there is any other information you think may be of use to inform the Secretariat's work on routinely collected pharmaceutical data, please comment below.

Annex 2- Country examples of how routinely collected data have been used to inform pharmaceutical regulation and policy

Case studies: Regulators and health systems using routine data in post-marketing studies

Table 5.1. EMA re-assessment of safety risks associated with testosterone treatment (TT)

Study	EMA-initiated study: EMA study on prescribing of testosterone in the primary care setting (Svendsen 2014) Studies in the published literature using RWD that informed EMA review: Baillargeon et al. 2014; Finkle et al. 2014; Shores et al. 2012; Tan et al. 2014; Vigen et al. 2013
Objective	EMA-initiated study by Svendsen 2014: to describe the extent and patterns of prescription of testosterone in a primary care setting in the European Union. Studies using RWD in the published literature: Baillargeon et al. 2014: Assess the risk of (MI) in older men receiving intramuscular testosterone Finkle et al. 2014: Assess the association between testosterone therapy (TT) and cardiovascular disease Shores et al. 2014: Assess the association between TT and mortality in men with low testosterone levels Tan et al. 2014: Assess the association between TT and MI or stroke Vigen et al. 2013: Assess the association between TT and all-cause mortality, myocardial infarction (MI) or stroke
Motivation	Referral of safety concerns by an EU member state, pursuant to Article 31 of Directive 2001/83/EC, to the EMA for review of the benefit-risk of testosterone-containing medicinal products in its approved indications.
Data	Svendsen 2014: EMA in-house databased of electronic health records (EHR) from 3 EU Member States France, Germany and the UK. Only UK data were used after preliminary analysis. The dataset includes anonymised EHR of 5,686,400 patients from 1990 onwards, covering patient diagnoses, test results and prescriptions collected through a representative panel of GPs, as well as demographic and lifestyle characteristics. Baillargeon et al. 2014: Various Medicare (US) datasets, combined to obtain a 5% nationally representative sample of Medicare beneficiaries, including demographic and enrolment information, claims for hospital stays, outpatient visits and physician services. Finkle et al. 2014: Truven Health MarketScan Commercial Claims and Encounters Database (US) include diagnoses, procedures and prescriptions from 2006 to 2010. Two cohorts of 55,593 testosterone therapy (TT) recipients and 167,279 recipients of phosphodiesterase type 5 inhibitors (PDE5I). Shores et al. 2012: Data on 1,093 male patients from the Consumer Health Information and Performance Set, a database of clinical records, of the US Veterans Administration (VA). Tan et al. 2014: EHRs from 39,937 patients seen between years 2009 and 2014 at 40 “Low T Centers” in the US. Vigen et al. 2013: EHR data from the US VA Clinical Assessment Reporting and Tracking (CART) program, including procedural data at the point-of-care for all procedures performed in the 76 VA cardiac catheterization laboratories.
Inclusion criteria	Svendsen 2014: None Baillargeon et al. 2014: Male Medicare beneficiaries aged 66 years or older and who were treated with intramuscular testosterone between 1997 and 2005 and who were not enrolled in both Medicare part A and part B for the 12 months before the first testosterone injection, who were not members of a health maintenance organization any time during the 12 months before the first injection, who did not have end-

	stage renal disease and did not use testosterone in the 12 months prior to the incident testosterone injection. Finkle et al. 2014: Male patients who received TT or PDE5I, had no history of myocardial infarction (MI) prior to the first prescription for TT or PDE5I, and had a minimum of 22 months of continuous enrolment for analyses with post-prescription follow-up intervals of 90 days, and 25 months for analyses with post prescription follow-up intervals of 91 to 180 days. Shores et al. 2012: Men older than 40 years who were treated at one of the VA medical centres and had total testosterone levels of 250 ng/d or less (8.7 nmol/liter) measured between 2001 and 2002 and did not have a history of prostate cancer, treatment with testosterone or antiandrogens. Tan et al. 2014: not specified Vigen et al. 2013: Male veterans who had a total testosterone level checked in the VA, had a total testosterone level less than 300 ng/dL and who underwent coronary angiography between 2005 and 2011, and who did not start TT prior to coronary angiography, did not start TT prior to having testosterone level checked in the VA and did not receive TT after an MI.
Outcomes of interest	Svendsen 2014: Prevalence and incidence of testosterone prescription in 2012 and between 1995 and 2012 by age and sex. Incidence of testosterone prescription among males by dosage form, indication (ICD chapter "F52: sexual dysfunction"; chapters "C, D and Z40: cancer"; and "not specified") and co-morbidity. Baillargeon et al. 2014: Hospitalisation for MI Finkle et al. 2014: Incidence of myocardial infarction (MI) following testosterone therapy (TT) compared to prescription of phosphodiesterase type 5 inhibitors (PDE5I). Shores et al. 2012: Total mortality in testosterone-treated compared with untreated men. Tan et al. 2014: Incidence of MI and stroke in the cohort compared to the Kaiser Permanente and Northern Manhattan Registry. Vigen et al. 2013: Time to all-cause death or hospitalization for MI or ischemic stroke.
Results	Svendsen 2014: Testosterone prescribing increased over time. In 2012, 0.27% of all males received testosterone, of which 17.6% were new users. Among new users, 29% received testosterone for sexual dysfunction, 8% for cancer and 63% for unspecified reasons. In 1995-2012, 0.22% of males received testosterone, of which 70.9% were new users. Among new users, 27% received testosterone for sexual dysfunction, 8% for cancer and 65% for unspecified reasons. Testosterone recipients in general have high rates of cardiac co-morbidities. Recipients for sexual dysfunction have more cardiac-related comorbidities and are older than other recipients. Recipients for cancer-related issues have more epilepsy, steroid responsive conditions and hypothyroidism. Baillargeon et al. 2014: There was no increased risk of MI in older men. After adjusting for demographic and clinical characteristics, hazard ratio (HR) of MI in the intervention group was 0.84 (95% CI 0.69 to 1.02) compared to the control group. For men in the highest quartile of the MI prognostic score, testosterone use was modestly protective with a HR of 0.69 (95% CI = 0.53-0.92), whereas there was no difference in risk for the first three quartiles. Finkle et al. 2014: In older men, and in younger men with pre-existing diagnosed heart disease, the risk of MI following initiation of TT prescription is substantially increased. In all subjects, the post/pre-prescription rate ratio (RR) for TT prescription was 1.36 (1.03 to 1.81). In men aged 65 years and older, the ratio of the rate ratios (RRR) for TT prescription relative to PDE5I was 1.90 (1.04, 3.49) and in men under age 65 years, excess risk was confined to those with a prior history of heart disease, with a RRR of 2.07 (1.05 to 4.11). Shores et al. 2012: TT was associated with decreased mortality, although residual confounding may be a source of bias. After adjustment for age, body mass index, testosterone level, medical morbidity, diabetes, and coronary heart disease, the hazard ratio of death in the treatment group was 0.61 (95% CI 0.42 to 0.88) compared to the control group.

	Tan et al. 2014: There is a protective effect of testosterone against MI and stroke. Rate ratios (RR) for MI in testosterone treated patients is 0.14 (CI 0.098 to 0.211) and for strokes 0.107 (CI 0.06 to 0.21). Vigen et al. 2013: At 3 years after coronary angiography, the unadjusted absolute risk difference was 5.8% (95% CI, -1.4% to 13.1%) between the TT therapy and the no TT therapy group. After adjusting for the presence of coronary artery disease, TT use as a time-varying covariate was associated with increased risk of adverse outcomes (hazard ratio 1.29; 95% CI, 1.04 to 1.58).
Policy impact	The PRAC concluded that the findings in the literature do not consistently show an increased risk of cardiovascular events and do not corroborate the signal of an increased risk associated with testosterone therapy. Taking all evidence into account, the signal for an increased cardiovascular risk was considered weak and inconclusive. The PRAC recognised that testosterone may cause severe complications in some patient sub-groups and that some uncertainty remains as to direct and indirect effects of testosterone on the cardiovascular system in general and in patients over 65 years of age, which should be investigated further. The PRAC requested that the market authorisation holders continue to monitor cardiovascular events and report findings of ongoing studies in periodic updated safety reports and that updates to the product information should be made to ensure that potential cardiovascular risks associated with testosterone use are addressed in all products approved (EMA, 2014b). The EMA Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed PRAC recommendations by consensus, which were implemented by member states where the medicines have market approval, and issued information on the review to patients and health care professionals (EMA, 2014a).

Source: Authors' compilation

Table 5.2. Post-market review of ezetimibe to review the cost-effectiveness in the context of the latest available evidence and best clinical practice in Australia

Study	Post-market review of ezetimibe (http://www.pbs.gov.au/info/reviews/post-market-review-ezetimibe, 2017
Objective	1. To review the current utilisation of PBS-listed ezetimibe and ezetimibe combination products. 2. Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the PBS and; 3. Collate and evaluate any recent clinical studies of ezetimibe that report on long term patient relevant outcomes, and use this data to review the cost-effectiveness of ezetimibe.
Motivation	Ezetimibe is listed on the PBS for the treatment of high cholesterol in certain patient populations. Ezetimibe is used to lower high cholesterol with the goal of reducing the risk of cardiovascular events such as heart attacks and stroke. In 2003, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of ezetimibe on the PBS based on effectiveness data available at the time. However, unlike ezetimibe, there is a large body of evidence that shows statins reduce low density lipoprotein cholesterol (LDL-C) concentrations, which translated to a lower risk of cardiovascular events and mortality. For the majority of patients, the PBS restrictions for ezetimibe require a trial of statins at maximum tolerated doses prior to prescribing ezetimibe, so that patients can derive maximum clinical benefit from statins. In November 2013, the PBAC expressed concern that the listing of ezetimibe with statin co-packs and combination products on the PBS may direct use away from optimal dose titration of statins. At the time, there were no studies reporting long term patient relevant outcome data for ezetimibe and PBS expenditure on the medicine was high. The PBAC recommended a Post-market Review of ezetimibe in August 2015, and the Minister for Health agreed to the Review in September 2015.
Data	Unit record level PBS data was extracted for all medicines listed under ATC C10 for the dates of supply of ezetimibe from 1 April 2012 to 31 March 2016, including the actual dispensing dates up to 31 July 2016. The PBS dataset was complete as it included all under co-payment prescriptions (i.e., the dispensed statins that are priced under the general co-payment threshold are included). It did not contain prescriptions written as private scripts or samples given to patients by doctors. The original 111,561,966 records were split into two datasets. The two datasets were subsequently merged in order to add the ATC5 codes to the corresponding PBS item codes. Further modifications were made, resulting in the final total number of records available for the primary analysis of 95,563,746 prescription records for 45,645 patients initiating treatment with ezetimibe (i.e. prescriptions for patients who were first dispensed ezetimibe or ezetimibe combination) between 1 April 2014 and 31 March 2015. The primary dataset (45,645 patients) was subdivided into Cohort 1 (6,938 patients, 15%) who had no prior lipid lowering therapy (LLT) in the previous 24 months and Cohort 2 (38,707 patient, 85%) who had at least one dispensing of LLT in the prior 24 months. In the sensitivity analysis, the number of ezetimibe initiator patients (i.e. patients who were first dispensed ezetimibe or ezetimibe combination between 1 April 2015 and 31 March 2016) was 54,599. The records were sorted by the supply date. The supply date was used in assigning other criteria in the course of data analysis (e.g. the period of continuous treatment).

Inclusion criteria	All patients who were dispensed PBS subsidised ezetimibe under ATC C10 between 1 April 2012 and 31 July 2016. The following records were deleted: Those corresponding to patients who were prescribed ezetimibe or ezetimibe combination prior to 1 April 2014 (N='13,155,888' records or 11.8%); and Duplicate records that involve the same drug of the same strength dispensed to the same patient on the same day (N='2,842,332' or 2.9%).
Outcomes of interest	Initiation, switching and continuation of PBS-listed ezetimibe and statin items was used to identify the following three groups of patients: new users of ezetimibe initiating ezetimibe in accordance with PBS restriction; those initiating ezetimibe not consistent with PBS restrictions; and the remainder for whom compliance with the PBS restrictions is unknown.
Results	The analysis identified 45,645 patients who commenced ezetimibe between April 2014 and March 2015. Of these, 6,938 (Cohort 1, 15 %) had no prior lipid lowering therapy (LLT) in the previous 24 months and 38,707 (Cohort 2, 85 %) had at least one dispensing of LLT in the prior 24 months. There was some uncertainty around compliance with PBS restrictions for some ezetimibe initiators due to insufficient information from PBS data on intolerance and contraindication to statins. The analysis linked all LLT pre and post ezetimibe at the individual patient level to classify patients in the following three groups: 46% appeared to have initiated ezetimibe in accordance with the PBS restriction 18.4% appeared to have initiated ezetimibe in a manner that was not consistent with the PBS restriction, and 34.8% initiated ezetimibe and compliance with the PBS restriction was unknown.
Policy impact	Based on the outcomes of this review, the PBAC recommended that a price reduction in the range of 18.4%-35.8% would be required to restore the cost-effectiveness of PBS-subsidised ezetimibe.

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Table 5.3. Assessment of link between Benfluorex and valvular heart disease in France

Study	Weill A. et al. (2010), Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus, Pharmacoepidemiology and drug safety; Vol. 19, pp. 1256–1262.
Objective	Assess the link between benfluorex and risk of valvular heart disease, motivated by safety alerts
Motivation	Safety alerts
Data	Health insurance claims (SNIIRAM) and hospital discharges (PMSI).
Inclusion criteria	All patients aged 40–69 years with reimbursement for oral antidiabetic and/or insulin in 2006 (1 048 173 patients). "Exposed Patients" were patients with at least one benfluorex reimbursement in 2006 (43 044 patients).
Outcomes of interest	Selected admission diagnoses of interest in 2007 and 2008 PMSI databases were valvular insufficiency for any cause, mitral insufficiency, aortic insufficiency, and valvular replacement surgery with cardiopulmonary bypass. Adjusted Relative risks (ARR) exposed/non-exposed were adjusted on gender, age, and history of chronic cardiovascular disease.
Results	Benfluorex in diabetic patients was significantly associated with hospitalization for valvular heart disease in the 2 years following benfluorex exposure. ARR of hospitalisation in 2007 and 2008 for any cardiac valvular: 3.1 [2.4–4.0], with a lower risk for patients with lower cumulative dose of benfluorex. ARR for mitral insufficiency and aortic insufficiency admissions were 2.5 [1.9–3.7] and 4.4 [3.0–6.6], respectively. ARR for valvular replacement surgery was 3.9 [2.6–6.1].
Policy impact	Benfluorex (Mediator®) was withdrawn from the market on November 2009, one month after results were communicated for the drug agency. This case led to changes in the drug legislation because it took a lot of time for recurring alerts to be taken into account by regulators.

Source: Authors' compilation

Case studies: Impact of routinely collected data on reimbursement and pricing policies

Table 5.4. Impact assessment of generic substitution and reference pricing for antipsychotics in Finland

Study	(Koskinen et al., 2015[85]) Time series analysis on the impact of generic substitution and reference pricing of antipsychotic drugs. Value in Health 18, pp1105–1112
Objective	To analyse the medium- to long-term impact of generic substitution and the reference price system on the daily cost of antipsychotics in Finland. The study assess additional impact of reference pricing over and above previously implemented generic substitution.
Motivation	Finland introduced generic substitution in 2003 and reference price system in 2009. There was lack of studies examining the impact of reference price system beyond the first year.
Data	Reimbursed prescriptions dispensed in pharmacies (Finnish Prescription Registry, The Social Insurance Institution)
Inclusion criteria	The data have 69 monthly values of the average daily cost for each of the studied antipsychotics (ketiapine, olanzapine, risperidone, aripiprazole), 39 months before and 30 months after the introduction of reference pricing
Outcomes of interest	Average daily cost
Results	According to the model, 2.5 years after the implementation of reference pricing, the daily cost of the studied antipsychotics was 24.6% to 50.6% lower than it would have been if reference pricing had not been implemented. The additional impact of reference pricing over and above previously implemented generic substitution was modest, less than 1 percentage point. Although the price competition induced by reference pricing decreased the prices of antipsychotics in Finland in the short-term, the prices had a tendency to stagnate or even to turn in an upward direction in the medium- to long-term. Furthermore, the additional impact of reference pricing over and above previously implemented generic substitution remained quite modest
Policy impact	In an attempt to tackle increasing reference prices, the calculation of reference prices changed in 2017. While the previous method added 1.50 EUR for products priced lower than 40 EUR and 2 EUR for products priced above 40EUR, the revised price calculation used the lowest-priced product in a reference price group added with 0.50 EUR.

Source: 2018 OECD Survey on routinely collected data

Table 5.5. Assessment of risk associated with Olmesartan based on routinely collected data in France

Study	Mezzarobba M., A. Weill and P. Ricordeau (2014), Exposition aux différents sartans et risque d'entéropathies - Compléments apportés à l'étude : Entéropathies associées à la prise d'olmésartan, CNAMTS-DSES-DESP.
Objective	Compare risks of enteropathy of all sartans
Motivation	In July 3, 2013, the FDA revised the labelling instructions of products containing olmesartans. This decision was based on a study published in 2012 and showing an increased risk of enteropathy in patients treated with olmesartans. Safety alerts were also reported in France. The French drug agency ANSM posted an information sheet on its website in July 2013 and announced continuous monitoring.
Data	Health insurance claims (SNIIRAM) and hospital discharges (PMSI)
Inclusion criteria	Original study and methods not available.
Outcomes of interest	Original study and methods not available.
Results	Increased risk of enteropathy with olmesartans which does not exist with other sartans.
Policy impact	In April 2015, the HAS Transparency Commission re-assessed all products containing sartans, following a request from the "Health Directorate" of the Ministry and an internally generated demand. Assessment reports mention the results of the observational study and conclude that these medicines should no longer be reimbursed. Delisting was announced for June 2016 but then postponed by six months to allow adjustments from patients and prescribers. From January 2, 2017 products containing olmesartans are no longer reimbursed.

Source: Authors' compilation

Table 5.6. Assessment of risks associated with combined hormonal contraceptives (CHC) based on routinely collected data in France

Study	Cnamts – DSES – DESP (2013), Risque d'embolie pulmonaire, d'accident vasculaire cérébral ischémique et d'infarctus du myocarde chez les femmes sous contraceptif oral combiné en France : une étude de cohorte sur 4 millions de femmes de 15 à 49 ans à partir des données du SNIIRAM et du PMSI, Rapport final du 26 juin 2013
Objective	To assess absolute and relative risks (RR) of pulmonary embolism (PE), ischaemic stroke (IS) and myocardial infarction (MI) according to the type of Combined hormonal contraceptives (CHC) with 1st, 2nd and 3rd generation of progestogens. 2nd generation - Levonorgestrel, Norethisterone, Norgestrel 3rd or 4th generation – Desogestrel, Gestodene, Norgestimate, Etonogestrel, Drospirenone, Dienogest, Chlormadinone, Nomegestrol, Norelgestromin
Motivation	Improve recommendations and practices
Data	Health insurance claims (SNIIRAM) and hospital discharges (PMSI)
Inclusion criteria	All women aged 15- 49 with at least one CHC reimbursed by health insurance between July 1, 2010 and December 31, 2011 (4 343 692 women, 2 962 857 person-year). Exclusion: Women with antecedents of cancer or thromboembolic events.
Outcomes of interest	1. Incidence rate of PE 2. Rate of IS 3. Rate of MI 4. Composite criteria associating EP, AVCi, IM. RR were estimated using Poisson regression and estimates were adjusted for age, deprivation index and status with respect to complementary Universal Health Insurance for the poorest women (12% of the study population), hypertension, diabetes, smoking (nicotine substitute reimbursement or hospital diagnosis related) and a visit to a private practice gynaecologist.

Results	**ARR (and 95% CI) for PE** (lévonorgestrel 30/40g EE as reference) were: 1.53 (1.27 to 1.87) for desogestrel/20, 1.74 (1.09 to 2.73) for gestodene/20, 0.74 (0.54 to 0.98) for levonorgestrel/20, 2.19 (1.84 to 2.61) for desogestrel/30-40 and 1.31 (0.79 to 2.03) for gestodene/30-40. **ARR for MI/IS** were 0.86 (0.67 to 1.11) for desogestrel/20, 0.41 (0.20 to 0.75) for gestodene/20, 0.75 (0.52 to 1.05) for levonorgestrel/20, 0.79 (0.57 to 1.06) for desogestrel/30-40, 1.02 (0.56 to 1.70) for gestodene/30-40 and 2,78 (1,81 to 4.01) for Norgestrel 50. **The dose** of 20 g (réf 30-40) was associated with a significantly lower risk for EP and IM respectively 0.73 (0.61 to 0.86] and 0.61 (0.36 to 0.98) Conclusion: This study reports similar results to those of recent large observational studies despite the limitations of database studies. Study found a significantly lower risk with levonorgestrel combined with EE at a dose of 20g, a combination not previously assessed in the Danish cohort.
Policy impact	A re-assessment of 3rd generation CHC by the HAS Transparency Commission and several votes of this commission between June 2012 and September 2012 finally led to the conclusion that these products' therapeutic value was insufficient to justify reimbursement by social health insurance. On October 1, 2012, the French drug agency ANSM published an information sheet for prescribers with recommendations to 1) prescribe 1st and 2nd generation CHC as a first step; 2) document risk-factors for any prescription of CHC; 3) inform women about thrombolic risks; 4) follow up women under CHC. In November 2012, the HAS published another information sheet for prescribers insisting on prescription of 1st and 2nd generation CHC as a first step. On June 26, 2013, the ANSM published an information sheet for consumers, with Questions & Answers. On January 3, 2013, the Minister of Health announced that 3rd generation CHC would no longer be reimbursed from March 31, 2013. http://social-sante.gouv.fr/actualites/presse/communiques-de-presse/annee-2013/article/pilules-de-3eme-generation

Source: Authors' compilation

Case studies: Potential indirect effects on use by informing clinical guidelines

Table 5.7. Monitor prescribing quality and behaviour, review on medicines used in management of attention deficit hyperactivity disorder (ADHD) in Australia

Report	Public Release Document on the ADHD: Utilisation Analysis, June 2015.Available on the PBS website at: http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2015-06/attention-deficit-hyperactivity-disorder-2015-06-prd
Objective	To review the utilisation of PBS-listed medicines used in the management of attention deficit hyperactivity disorder.
Data	Australian Government prescription claims database and authority approvals data.
Outcomes of interest	The number of patients treated with PBS medicines for ADHD has risen steadily. Rates of prescribing varied across states and territories. There was use in children aged 5 years and under receiving prescriptions for an ADHD medicine and an antipsychotic medicine on the same day.
Policy impact	The Pharmaceutical Benefits Advisory Committee (PBAC) considered the ADHD report from its DUSC in July 2015. The PBAC was concerned that children aged 5 years and younger were receiving an antipsychotic. The PBAC considered that the practice of using antipsychotics for behaviour modification in this patient group was inappropriate. At the request of the PBAC, the DUSC report be provided to the National Prescribing Service to support initiatives to improve the quality use of ADHD medicines. For further information, the PBAC outcome statement on its consideration of the DUSC report can be viewed at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/pbac-outcomes-2015-07

Source: 2018 OECD Survey on routinely collected data

Table 5.8. Assessment of appropriateness of medicine use among >65 years population in Finland

Study	(Leikola et al., 2011[86])Potentially inappropriate medication use among Finnish non-institutionalized people aged of 65 years or more. A register-based, cross-sectional, national study. Drugs and Ageing, Vol 28, pp 227-236
Objective	To determine the prevalence of potentially inappropriate medicine use according to the Beers criteria, independent of diagnoses, among Finnish non-institutionalized elderly population aged of 65 years or more, and the reimbursement cost of these medications.
Motivation	There was lack on data on prevalence of potentially inappropriate medicine use in an entire national non-institutionalized elderly population and the reimbursement costs for those medications.
Data	Reimbursed prescriptions dispensed in pharmacies (Finnish Prescription Registry, The Social Insurance Institution)
Inclusion criteria	The entire non-institutionalised population aged of 65 years or more in 2007 in Finland
Outcomes of interest	The number of persons who received reimbursements for each potentially inappropriate medicine(PIMs) according to the Beers 2003 criteria and the total annual reimbursement costs.
Results	Of the non-institutionalized population aged of 65 years or more in Finland (n=' 841' 509), 14.7% (n = 123 545) had received PIMs according to the Beers 2003 criteria. Temazepam >15 mg/day was clearly the most commonly reimbursed PIM (4.4% of the population aged 65 years or more), followed by amitriptyline (2.0%) and diazepam (1.8%). The Social Insurance Institution reimbursed €2.9 million for PIMs, which was 0.7% of the total drug reimbursements (€421 million) for people aged 65 years or more in Finland in 2007.
Policy impact	It was concluded, that while the use of PIMs was less than in several previously published large-scale studies in other countries and reimbursement costs were modest, benzodiazepines were commonly used and actions to improve medication safety should target reducing their use. This and several other studies have indicated the problematic medicine use especially in the elderly in Finland. For example long-term use of benzodiazepines has started to decrease since 2008.

Source: 2018 OECD Survey on routinely collected data

Table 5.9. Assessment of comparative effectiveness of statins in France

Study	Neumann A. et al. (2014), Comparative effectiveness of rosuvastatin versus simvastatin in primary prevention among new users: a cohort study in the French national health insurance database, Pharmacoepidemiology and drug safety, Vol. 23, pp. 240–250
Objective	Compare effectiveness of rosuvastatin and simvastatin prescribed at doses with close LDL-cholesterol-lowering potency in primary prevention on all-cause mortality and cardiovascular and cerebrovascular diseases.
Motivation	Not specified
Data	Health insurance claims (SNIIRAM) and hospital discharges (PMSI)
Inclusion criteria	All patients with no prior cardiovascular and/or cerebrovascular diseases, aged 40–79 years, who initiated statin therapy with rosuvastatin 5mg (106 941 patients) or simvastatin 20 mg (56 860 patients) in 2008–2009 in general practice. Follow-up started after a 1-year period used to select patients who regularly received the initial treatment. In an intention-to-treat analysis, patients were followed up to December 2011. In a per-protocol analysis, they were censored prematurely when they discontinued their initial treatment. Adjustment for baseline covariates (age, deprivation index, comedications, comorbidities, prior hospital admissions) was carried out by a Cox proportional hazards model. In the per-protocol analysis, estimation was done by "inverse probability of censoring weighting" using additional time-dependent covariates. Analyses were gender-specific.
Outcomes of interest	1) all-cause mortality and 2) the composite of all-cause mortality and hospitalization for ischemic heart disease or ischemic stroke
Results	For both genders and both types of analyses, the difference in incidence rates of mortality and/or cardiovascular and cerebrovascular diseases between rosuvastatin 5mg and simvastatin 20mg users was not statistically significant after adjustment. The results of this real-life study based on medico-administrative databases do not support preferential prescription of rosuvastatin compared with (cheaper) simvastatin for primary prevention of cardiovascular and cerebrovascular diseases.
Policy impact	Unknown

Source: Authors' compilation

Table 5.10. Assessment of statin use in prevention of cardiac events in patients with ischaemic heart disease in Israel based on routine data collected by Clalit

Study	Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment (Leibowitz et al. 2016)
Objective	To assess the association between levels of low-density lipoprotein cholesterol (LDL-C) achieved with statin treatment and cardiovascular events in adherent patients with pre-existing ischemic heart disease.
Motivation	International guidelines recommend treatment with statins for patients with pre-existing ischemic heart disease to prevent additional cardiovascular events but differ regarding target levels of low-density lipoprotein cholesterol (LDL-C). Trial data on this question are inconclusive. Nevertheless, there has been a push to reduce LDL-C treatment targets in secondary prevention of cardiovascular disease to 70 mg/dL for all patients.
Data	Data for all Clalit Health Services members from the Clalit data warehouse. Anonymous patient data were compiled from EHR, the Clalit chronic disease registry, hospital discharge summaries, and pharmacy and laboratory records. Demographic data were obtained from the Israeli Central Bureau of Statistics and the Ministry of Internal Affairs. The final study population comprised 31,619 patients who were at least 80% adherent to statin treatment and 54,884 patients who were at least 50% adherent. Estimates were made between non-matched treatment groups using a proportional hazards model adjusted for clinical and socio-demographic variables and between propensity-score matched treatment groups.
Inclusion criteria	Patients with ischemic heart disease and requiring secondary prevention, aged 30 to 84 years, treated with statins for at least one year before the first serum LDL-C value measured at any time between 2009 to 2013, and at least 80% adherent to treatment or, in a sensitivity analysis, at least 50% adherent. Patients with active cancer or metabolic abnormalities were excluded.
Outcomes of interest	Time to major adverse cardiac events (MACE), including acute myocardial infarction, unstable angina, stroke, angioplasty, bypass surgery, or all-cause death.
Results	Patients with LDL-C levels of 70 to 100 mg/dL taking statins had lower risk of adverse cardiac outcomes compared with those with LDL-C levels between 100 and 130 mg/dL, but no additional benefit was gained by achieving LDL-C of 70 mg/dL or less. Incidence of adverse outcomes, adjusted for socio-economic and clinical variables, was not different between low and moderate LDL-C (hazard ratio 1.02; 95% CI, 0.97 to 1.07) but was lower with moderate vs high LDL-C (hazard ratio 0.89; 95% CI 0.84 to 0.94). Among 54,884 patients with at least 50% statin adherence, the adjusted hazard ratio was 1.06; 95% CI, 1.02 to 1.10 in the low vs moderate groups and 0.87; 95% CI 0.84 to 0.91 in the moderate vs high groups.
Policy impact	Based on the result of this study, Clalit refrained from lowering treatment targets and maintains that achieving LDL-C levels below a threshold of 100 mg/dL is sufficient. National news channels and papers have covered results of this study extensively and impact on policy was still unfolding at the time of writing of this report (personal communication with Prof Ran Balicer, Director of the Clalit Research Institute).

Source: Authors' compilation.

Table 5.11. Proactive monitoring of the safety and effectiveness of the pertussis vaccine in pregnant women

Study	(Donegan, King and Bryan, 2014[87])Safety of pertussis vaccination in pregnant women in UK: observational study (BMJ; Vol 349: g4219) (Amirthalingam et al., 2014[88])Effectiveness of maternal pertussis vaccination in England: an observational study. (Lancet; Vol 384: pp 1521-8) (Amirthalingam et al., 2016[89])Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction (Clin Infect Dis; Vol 63: pp S236-43)
Objective	To monitor the safety and effectiveness of the acellular pertussis-containing vaccine, Repevax, in pregnant women administered during the temporary vaccination campaign.
Motivation	A peak in pertussis in England led to the development of a vaccination programme targeting pregnant women. The vaccine had not been used extensively in pregnancy, therefore authorities introduced close monitoring of the vaccine's safety and effectiveness.
Data	Data from the Clinical Practice Research Datalink (CPRD) and data from the NHS England Hospital Episodes Statics data (HES) alongside reported cases of laboratory confirmed pertussis captured through national surveillance routes
Inclusion criteria	All pregnant women including those receiving a pertussis vaccination while pregnant
Outcomes of interest	Rate and coverage of vaccination in pregnancy Adverse outcomes following vaccination (stillbirth, maternal and neonatal death, pre-eclapsia or eclampsia, haemorrhage, fetal distress uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, and neonatal renal failure) Time to delivery Incidence of laboratory confirmed pertussis
Results	Safety: A cohort of over 20,000 vaccinated women, and a matched historical unvaccinated cohort, showed no increased risk of any of the pre-specified adverse events of interest. Effectiveness: First published analysis, vaccine effectiveness based on 82 confirmed cases in infants born from Oct 1, 2012, and younger than 3 months at onset was 91% (95% CI 84 to 95). Second published analysis, vaccine effectiveness against infant deaths was estimated at 95% (95% confidence interval, 79%–100%)
Policy Impact	Supported national continuation of the vaccination programme Used in patient information leaflets Used in amendments to vaccine product licence regarding use in pregnancy Contributed the first major comparative international data on the safety and effectiveness of such a vaccination programme

Source: 2018 survey on routinely collected data

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