Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 8.4
Real-life data and learning from practice to advance innovation

By Tjeerd-Pieter van Staa¹,², Olaf H. Klungel¹

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¹Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands
²London School of Hygiene & Tropical Medicine, London, United Kingdom

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1. **Introduction**

The costs of pharmaceutical R&D are high, with clinical trials being a major component of these development costs. There is an urgent need to address therapeutic gaps in order to be able to respond to unmet medical needs. To help resolve this problem, there is a need to increase efficiency and to bridge bench and clinical research with real-world practice. Making better use of real-world data can improve the efficiency of the whole medicine development chain: HTA bodies, regulators, clinicians and patients will be able to make better-informed decisions, and companies will be able to design better and more efficient development strategies that provide the appropriate evidence to decision makers.

Additionally, data obtained from health information systems can be used to support priority setting, detect safety problems and assess the real-world effectiveness of medicines. Moreover, policy initiatives such as adaptive licensing, value-based pricing and comparative effectiveness studies are critically dependent on the efficient use of Electronic Health Record (EHR) data. However, the resources available in Europe are fragmented, and good quality data are often only available for limited disease areas or geographic regions.

In the 2004 Priority Medicines Report, the use of electronic health records was highlighted as an area of high importance. It was suggested as “a way of creating post-marketing ‘randomized epidemiology’ studies to better understand comparative effectiveness and cost-effectiveness.” Although progress has been made since then, the potential is still largely unfulfilled.

Real-world data are now more widely available than ever before and offer new opportunities for research and health systems development. Information in the health care system is increasingly processed electronically in many countries across the world. Databases that collate health care information from larger numbers of patients are becoming available for research. The information that is available for research in these databases has been changing over time and the possible contribution of health care databases to pharmaceutical innovation has been evolving.

We will provide examples in this background paper on how these databases can inform priority setting and support pharmaceutical innovation by assisting in, amongst others, the prioritisation of research needs, better disease understanding, safety monitoring, comparative effectiveness research and the evaluation of health care policies. Examples will be given on how these health care databases can help to identify the greatest challenges with pharmaceutical treatments and test their effects in real life.

**List of abbreviations**

- **EHRs**: Electronic Health Records
- **RCT**: Randomised controlled trials
2. Limitations of randomised clinical trials and market authorization process

New health care interventions (such as medicines and devices) are typically only given authorization for use in routine clinical practice after randomised clinical trials (RCTs) have shown positive benefit-risk ratio. These interventional studies are in general conducted using strict eligibility criteria with many inclusion and exclusion criteria and with close instructions of study patients how to use the medications. RCTs often exclude patients based on age, gender, co-morbidity and geographical location (also see the Background Papers to Chapter 7.1 and Chapter 7.3). In contrast, patients in routine clinical practice are diverse, with varying disease histories and co-medications and they do not always comply with instructions and persist with treatment over time. Medicine use in clinical practice frequently differs widely from the (pre-approval) clinical trial settings. Selective COX-2 inhibitors provide an example of the challenges in generalising evidence from authorization RCTs to routine clinical practice. The main RCTs of rofecoxib and celecoxib that were used to obtain the marketing authorization restricted study eligibility to patients with severe osteoarthritis or rheumatoid arthritis who were expected to use the study drug daily for the duration of the studies (six to nine months).\(^2\)\(^3\) However, an analysis found that the large majority of patients using selective COX-2 inhibitors in routine clinical practice would not have been eligible for these main RCTs as they did not have severe osteoarthritis or rheumatoid arthritis and did not use these medicines every day for a number of months.\(^4\) The results of authorization RCTs are, therefore, not always generalizable to patients in routine clinical practice.\(^5\)

Authorization RCTs typically assess the efficacy of a medicine, that is, the effects under ideal circumstances. On the other hand, effectiveness concerns the effects of a medicine under routine clinical circumstances.\(^6\) There are various reasons for differences between efficacy and effectiveness. One reason leading to these differences is the adherence of patients to the medication and the recommended dosage instructions. An example is alendronate; in pivotal RCTs for drug approval 89% of study participants were still using the study drug after three years.\(^7\) In real life, however, only about 35% were still using alendronate after three years.\(^8\) Another reason for the discrepancy between efficacy and effectiveness are differences in dosages. The daily dose of COX-2 inhibitors rofecoxib and celecoxib was about one-third in routine clinical practice compared to that in the authorization RCTs.\(^4\) A challenge in the generalizability of evidence from RCTs to real life concerns patients who were not eligible for the RCTs. It has been proposed recently that all patients aged 50 years or older should receive a statin given their cardiovascular risk. However, most of these patients would not have been eligible for the statin RCTs, as inclusion was restricted to individuals with high cholesterol blood levels and not based on high cardiovascular risk.

The current requirements for drug authorization do also not always provide the answers clinicians’ need, as exemplified by the high levels of off-label prescribing (i.e., prescribing not consistent with the authorization license). A Canadian study evaluated the treatment indications in the electronic health records (EHRs) for 253 347 electronic prescriptions. It found that the prevalence of off-label use was 11.0%; of the off-label prescriptions, 79.0% lacked strong scientific evidence. Off-label use was highest for central nervous system drugs (26.3%), including anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%).\(^9\)
3. Examples of EHR databases

Today, electronic health records (EHRs) are an increasingly important source of information to capture the real-world setting. Electronic Health Records can be defined as a “longitudinal collection of electronic health information about individual patients and populations.”10 This includes information about diagnosis (e.g. laboratory tests), treatment (e.g. dispensing of medicines) and outcomes of patients (e.g. hospitalization and mortality). For some research purposes, these data can be linked to other non-health datasets (e.g. data about employment or socio-economic information) to generate a comprehensive picture.

Real-life data on medicine use at the patient level first became available during the 1980s when administrative information about medicine use and health system activities was first stored at a significant level. Over recent decades, innovation in information technology (IT) infrastructure and capabilities and methodological refinements have played an important role in the increasing capabilities and potential of using real-life data to answer questions relevant for innovation.

There are currently over 300 EHR databases in 45 countries with different characteristics as recorded by the International Society for Pharmacoeconomics and Outcomes Research.11 Examples of EHR databases that are being widely used for research include the Clinical Practice Research Datalink (previously named the General Practice Research Database) in the United Kingdom, the Dutch PHARMO Record Linkage System and the national databases in Sweden and Denmark. The Clinical Practice Research Datalink collates the anonymised EHR information for over five million patients currently registered at a participating general practice. This EHR database has been linked individually and anonymously to other electronic health care datasets, including the national registry of hospital admissions in England (Hospital Episode Statistics), the national death certificates (with primary and secondary cause of death) and prospective disease registries, such as the cancer and cardiovascular disease registries.12 More recently, the Dutch public-private partnership Top Institute Pharma Mondriaan project established an infrastructure for linkage and enrichment of routine health care data in order to enhance research on benefits and risk of medicines.13 Currently, data from multiple sources such as general practice (one million patients), community pharmacy (11 million patients), hospital pharmacy and laboratory (100 000 patients) can be linked using privacy enhancing technology such as application of trusted third parties. Using this infrastructure the BIOLINK-NL project is currently developing a national infrastructure for linkage of social and medical registries to biobanks which will enormously enhance the possibilities for research on molecular biomarkers of pharmaceutical response (both harmful and beneficial) and the development of personalised treatment. In Denmark and Sweden, each national health care system provides universal coverage to all residents (5.5 million inhabitants in Denmark and 9.2 million inhabitants in Sweden). Health care coverage includes visits to general practitioners, specialists, hospital admissions, and outpatient visits; where pharmaceutical costs are either partially or completely covered. A centralised civil registration system has been in place in each country for many years, allowing for personal identification of each person in the entire population and for the possibility of linkage to all national registries containing civil registration numbers, e.g., patient registry, cancer registry, prescription databases, and registry of causes of death.14
4. Stages in the development of EHR databases

Table 8.4.1 outlines a simplified representation of stages in the development of EHR databases in the United Kingdom. Initial use of electronically obtained health care data mostly consisted of aggregate analyses of administrative data such as hospital admission data. When clinicians started to use computers for record keeping, it was realised that these data could be very useful for analyses of individual patient data. Research databases that collated the anonymised EHRs were created. An example is the VAMP research database which eventually changed into the Clinical Practice Research Datalink. The first use of these database consisted of analyses of safety outcomes of medicines. Over time, the richness and completeness of EHR databases has increased. Linkages between different EHR datasets were implemented (an example is the linkage between data from general practitioners and hospitals). Also, more information was shared electronically between different parts of the health care system. An example is the laboratory data; over the last decade, laboratory results have been communicated electronically and then loaded automatically into the EHR. This background paper will describe how EHR databases can be used to advance our knowledge of medicines that are used in routine clinical practices and inform policymaking and facilitate innovation about how and what interventions are being used in clinical practice.

<table>
<thead>
<tr>
<th>Time-period (approximate)</th>
<th>Development of EHR databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s onwards</td>
<td>Data collected for administrative purposes (such as hospital admission data and death certificates); mainly used for aggregate analyses</td>
</tr>
<tr>
<td>1990s onwards</td>
<td>Clinicians starting to use computers for record keeping (replacing paper records) and data collated into research database; mainly used for drug safety monitoring</td>
</tr>
<tr>
<td>2000s onwards</td>
<td>Linkages between various EHR databases and administrative data (e.g. claims for payments); mainly used to obtain complementary information or to validate outcomes</td>
</tr>
<tr>
<td>2010s onwards</td>
<td>Enrichment of routinely collected data by prospective data collection within EHR databases (e.g. collection of blood samples for genetic analyses or patient questionnaires)</td>
</tr>
<tr>
<td>2010s onwards</td>
<td>Introduction of randomisation at the point of care using the EHR database to identify potentially eligible patients and for follow-up of major clinical outcomes (i.e., pragmatic and cluster trials); mainly used to evaluate the effects of medicines in routine clinical practice</td>
</tr>
</tbody>
</table>

5. Challenges with using EHR databases

Since the 2004 Priority Medicines Report many initiatives have been taken to move forward the development of EHRs. However, translating the vision presented above into feasible and sustainable models that are applicable independent of country or health care setting is a major challenge.
EHR databases are currently mostly used for non-interventional (observational) studies in which clinicians determine the treatment allocation (rather than randomisation). Confounding is a major concern in observational studies; it means that observed differences between comparison groups are not caused by the exposure of interest but by unevenly distributed risk factors. As an example, observational studies suggested major reductions in the risk of cardiovascular disease by hormone replacement therapy while this was not confirmed in a large randomised RCT. There is evidence that hormone replacement therapy is given preferentially to healthier women. Observational researchers often seem to assume that it is sufficient to enter potential confounders into a statistical model in order to resolve confounding. Advanced statistical techniques (such as propensity score matching) are becoming more popular recently. But statistical techniques suffer from the same limitation that they cannot overcome unquantifiable or poorly recorded confounders. Instrumental variables may potentially control for unobserved confounding, though the strong assumptions underlying this method are often limiting its widespread application. However, the reverse assumption that observational studies are always fatally flawed may also not be correct. The eminent epidemiologist Jan Vandenbroucke has argued that observational studies should be restricted to questions that meet the underlying assumption that exposure allocation is unrelated to the outcome. As an example, people who start smoking do this for reasons unrelated to the risk of lung cancer. Consistent with this, risk estimates for adverse events were found to be similar between randomised RCTs and observational studies. An analysis of beneficial effects of medicines found frequent differences in risk estimates between RCTs and observational studies.

Data quality is of course very important and not all clinical outcomes can be measured accurately solely from the data recorded in the EHRs. Data may be missing and not measured and medical diagnostic information may be coded incorrectly. Furthermore, not all EHR databases will be of sufficient quality for research. Three dimensions of data quality may be fundamental: correctness, completeness and currency. Correctness refers to whether the information in a study is valid. Completeness refers to whether all required information is available or not. Currency relates to the time period between occurrence of an event and date of recording. Historically, the validations of EHR data have focused on the comparison of paper records and electronically recorded data. With the demise of paper records, such validations are increasingly being replaced by comparisons between linked EHR databases. As an example, a recent study compared cancer recording in the records of general practitioners, hospital records, death certificates and cancer registries and found considerable discrepancies in cancer recording between these different data sources. As data in linked databases are recorded for different purposes and using different systems, these comparisons can be challenging. There is a clear research need for developing and adopting systematic, statistically based methods of data quality assessment. Furthermore, the development of common data models and dictionaries could simplify research across different EHR databases.

EHR databases may not contain all the information that is needed for research. Data on prescribing in hospitals or specialist medicines such as biologics are rarely recorded in EHR databases but may be captured in dispensing databases. Anonymous linkages between registries and EHR databases provide opportunities to enrich research data. In addition to lifestyle factors, patient-centred outcomes are often incompletely recorded in EHR databases. But if patients can be approached through the clinician, these data can be obtained. As an
example, an ongoing study collects questionnaire information about employment histories in order to assess the health risks and benefits of extended working life. This study will examine the inter-relation of changes in employment as reported in patient’s questionnaires and changes in health as recorded in the EHR.23

6. Opportunities for innovation and learning from practice using EHR databases

EHRs are emerging technologies with increased adaptation and use in health care. While EHR databases will not provide answers to all questions, there are substantial opportunities in several areas of research that can inform policy decisions. A few examples of these are listed below and in Table 8.4.2.

6.1 Prioritize research needs

An important role of EHR database is to identify and measure research needs. These could include measurement of the level of off label medicines use and adherence to treatment guidelines. An example is a study of over 600,000 children that reviewed paediatric prescription patterns and reported on off-label medicine use in children.25 A study linking an in-patient hospital registry and the EHRs of general practitioners found that clopidogrel treatment initiated in hospital is frequently discontinued in primary care despite the recommendations in treatment guidelines. Discontinuation of clopidrogrel was associated with increased risks of mortality and recurrent myocardial infarction.26

A study that utilised pharmacy records assessed the quality of statin treatment and found that only 41% of patients that started with a statin received the first choice (simvastatin) according to the guidelines at that time.24 Research in the variability of health care between clinicians can highlight important levels of uncertainty with the result that patients can be treated differently. An example is the study that found that the prescribing of antibiotics to patients with chronic obstructive pulmonary disease experiencing exacerbations varied substantially (from 29% and 88%).27 This study supports the need for a large scale pragmatic RCT to evaluate the effects of antibiotics in this condition. If antibiotics would be effective in this condition, a large number of patients would be treated sub-optimally. If they are ineffective, antibiotics are being prescribed unnecessarily contributing to antibiotic resistance. A RCT has been started in order to test the feasibility of recruiting patients with COPD exacerbations at the point of care during consultation and then randomising patients to antibiotics or usual care. The EHR databases (using data from general practitioners, hospital admissions and death certificates) will be used to measure hospital admission over three months and long-term incidence of mortality.32
Table 8.4.2: Examples of different areas of research using EHR databases

<table>
<thead>
<tr>
<th>Area of research</th>
<th>Type of research</th>
<th>Example of a study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prioritize research needs</td>
<td>Drug utilisation studies</td>
<td>Cohort study in three European countries using EHR databases to assess drug use in children\textsuperscript{25}</td>
</tr>
<tr>
<td></td>
<td>Identify failures of interventions in routine clinical practice</td>
<td>Clopidogrel treatment initiated in hospital is frequently discontinued in primary care\textsuperscript{26}</td>
</tr>
<tr>
<td></td>
<td>Measure variability in interventions between clinicians</td>
<td>Considerable variability in the chance that a patient with a exacerbation of chronic obstructive pulmonary disease receives an antibiotic, dependent on which clinic is visited\textsuperscript{27}</td>
</tr>
<tr>
<td>Disease understanding</td>
<td>Disease co-morbidity network</td>
<td>Co-occurrence of different disease and prognosis of connected diseases\textsuperscript{28}</td>
</tr>
<tr>
<td>Identifying pharmaceutical gaps</td>
<td>Uptake and outcomes of pharmaceuticals</td>
<td>Use of bisphosphonates associated with fracture risk reductions after six to 12 months of treatment but only 58% of patients were treated for at least one year.\textsuperscript{8}</td>
</tr>
<tr>
<td>Safety of medicines</td>
<td>Safety monitoring</td>
<td>Previous studies reported increased risks of cancer with insulins. Study of users of different classes of diabetes medications found substantive biases without evidence for an increased cancer risk\textsuperscript{29}</td>
</tr>
<tr>
<td></td>
<td>Monitoring of regulatory actions</td>
<td>Study found that regulatory advice (to prescribe selective COX-2 inhibitors to patients at high risk of gastrointestinal disease but low risk of cardiovascular disease) was not followed\textsuperscript{30}</td>
</tr>
<tr>
<td></td>
<td>Research on pharmacogenetics and biomarkers</td>
<td>Recruitment within the Clinical Practice Research Datalink of 150 cases with statin myopathy and 500 control statin users</td>
</tr>
<tr>
<td>Comparative effectiveness</td>
<td>Observational studies</td>
<td>Hypertension treatment was relatively as effective in routine clinical practice as in RCTs, but fewer patients needed to be treated in real-life practice compared to RCTs to prevent a stroke\textsuperscript{31}</td>
</tr>
<tr>
<td></td>
<td>Pragmatic RCTs</td>
<td>Recruitment at the point of care randomising patients with high risk of cardiovascular disease between simvastatin and atorvastatin; follow-up for heart attacks using records of general practitioners, hospitals, death certificates and disease registry\textsuperscript{32}</td>
</tr>
<tr>
<td>Policy of treatment allocation</td>
<td>Risk prediction and identification of patients at high risk</td>
<td>Individual prediction of cardiovascular risk using EHR data. Used for screening to identify patients that should be treated with statins\textsuperscript{33}</td>
</tr>
<tr>
<td></td>
<td>Cluster trials randomising clinics between different policies</td>
<td>If a patient resenting with symptoms of respiratory tract infection, intervention clinics get an electronic prompt promoting no antibiotic prescribing or delayed antibiotic prescribing instead of immediate prescription. Clinics randomized to control do not get this reminder\textsuperscript{34}</td>
</tr>
<tr>
<td>Decision-making</td>
<td>Cost-effectiveness modelling</td>
<td>Model based on absolute risks as derived from the EHR database and relative drug effects as derived from RCTs. Study found that cost-effectiveness of selective COX-2 inhibitors was substantially worse compared to models that only used RCT data\textsuperscript{4}</td>
</tr>
<tr>
<td></td>
<td>Risk-benefit modelling</td>
<td>The benefit of selective COX-2 inhibitors in reducing the frequency of upper GI events may be offset by their cardiovascular harm, particularly in patients with risk factors for cardiovascular disease\textsuperscript{35}</td>
</tr>
</tbody>
</table>
6.2 Disease understanding

A recent review suggested that in the near future, EHR databases will impact significantly how we discover and develop safe and efficacious medicines. Novel disease relationships could be identified using EHR data. Hidalgo analysed EHRs of over 32 million patients to analyse the relationships between different diseases. They found that a disease that is connected to many other diseases tended to have worse prognosis compared to diseases that were less connected.

6.3 Identifying pharmaceutical gaps

EHR databases are routinely being used to measure the uptake and outcomes of medicines. Persistence (i.e., extent of long-term use) is often evaluated for treatments that need to be taken long-term. As an example, only one in four patients are using bisphosphonates for more than five years, despite the fact that their risk for fracture remains elevated; about 40% of the patients will stop this treatment within one year. Increased risks of osteoporotic and hip/femur fractures were found in patients with low compliance to bisphosphonates. This study highlights the need for innovation in ensuring persistence of use. Bisphosphonates may be effective medicines, as found in RCTs, but their full potential in reducing fractures is not being realised. Together with non-persistence suboptimal response to treatments can also be explained by other factors (e.g. environmental, genetic, clinical) and highlights another pharmaceutical gap; the exploration of the reasons for heterogeneity between individual patients in treatment response.

6.4 Safety of medicines

EHR databases have been used historically mostly for drug safety studies and the first studies were published over 25 years ago. These studies are widely recognised as being important for the detection and monitoring of adverse effects of medicines. A recent example of a safety study is an analysis of the cancer risks of patients initiating different classes of diabetes medicines. This study was conducted because initial studies reported increased risks of cancer with insulins which triggered substantial concern about the safety of these medicines. However, there was no evidence in this study of either beneficial or adverse effects of glucose-lowering agents on cancer risk.

EHR databases can provide information on the possible magnitude of risks of a known side-effect overall and in subgroups of patients. Such information can help to inform whether the side-effect may occur in e.g. one per 100 patients or one per 1000 patients and whether these risks may be substantially increased in certain patient groups or exposure characteristics (e.g., increased risks following treatment initiation or with long-term treatment). Spontaneous reporting systems of suspected side-effects can not provide such quantitative information as the level of under-reporting and the characteristics of users and size of the population are typically unknown. Of course, these analyses of crude incidence rates may not provide evidence of a causal relationship between increased incidence of adverse outcomes and the medicine, given the possibility of confounding. Such analyses should be viewed as the first step in reviewing whether further more detailed analyses are required.

There has been recent controversy in Europe around the risk of deep venous thrombosis due to cyproterone 2 mg in combination with 35 µg of ethinyl estradiol, which was being used for acne and oral contraception. Following a review of ten spontaneous case reports, the
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Dutch regulatory authority advised that women should no longer initiate this medicine but should not stop the treatment. Rather than communicating the number of spontaneous reports, it could have been useful to also communicate the possible levels of excess risks shortly after starting treatment and with long-term treatment as measured in EHR databases.

More recently, EHR databases are being used increasingly for pharmacogenetic research. A recent study identified patients who were using statins and developed rhabdomyolysis or highly elevated levels of creatine phosphokinase. The clinician then approached the patients and requested a blood or saliva sample. This system allows for almost “real-time” recruitment of patients who used a medicine of interest and developed a major side-effect, allowing prospective monitoring of both new and older medicines. (See also Chapter 7.4)

6.5 Risk prediction

EHR data are now being used to predict long-term risks of disease. An example is the QRISK score that predicts 10-year risk of cardiovascular disease using the routinely collected EHR data. Treatment guidelines in the United Kingdom now advocate that statins are initiated in patients with higher risks of cardiovascular disease as determined by risk scores such as QRISK.

6.6 Comparative effectiveness

Comparative effectiveness is the comparison of the beneficial and harmful effects of interventions in real life. This is defined as “the extent to which an intervention does more good than harm compared to one or more alternative interventions for achieving the desired results when provided under the usual circumstances of health care practice.” There is increasing interest in comparative effectiveness as this can inform e.g. reimbursement policies. A recent study from the Cardiovascular Research Network Hypertension Registry to compare the incidence of heart attacks, heart failure and stroke between different types of β-blockers. It found that there were no statistically significant differences in incident cardiovascular events between atenolol and metoprolol tartrate. The authors of this study concluded that large registries may be useful for addressing comparative effectiveness questions that are unlikely to be resolved by RCTs due to e.g. lack of statistical power.

A recent development is to conduct pragmatic RCTs within EHR databases providing an assessment of the comparative effectiveness in a randomised method. Patients are recruited at the point of care, randomised among routinely available interventions and then followed unobtrusively using the electronic health care database. An on-going RCT recruits patients indicated for statin treatment. The EHR database is used to identify patients at high risk of cardiovascular disease. After eligibility review by the clinician and informed consent, patients are then randomised between simvastatin and atorvostatin. Study participants are then followed for persistence to statin treatment and for major clinical outcomes using the EHR data. Myocardial infarctions are measured using the records of the general practitioner and linked data from hospitals, a disease registry and death certificates. The randomisation ensures that baseline differences and confounding is reduced.
6.7 Evaluation of health care policies

Health care policies, such as interventions reducing the rate of antibiotic prescribing, could be evaluated and tested in cluster trials. Entire areas or health service organisational units are randomly allocated to intervention or control groups in cluster trials, with outcomes evaluated for individuals within each cluster. A cluster trial has recently been completed evaluating antibiotic prescribing for respiratory tract infections. Electronic prompts had been developed based on recommended clinical practice guidelines to be activated during consultations for respiratory tract infections in the selected age range. The electronic prompts promoted no antibiotic prescribing or delayed antibiotic prescribing instead of immediate prescription. The prompts specifically incorporated recommendations from the recent guidelines on antibiotic prescribing in respiratory illness. During consultations with patients presenting with symptoms of respiratory tract infection, primary care professionals received electronic prompts reminding them of recommended standards of care in respiratory tract infections. The prompts also provided supporting information and links to evidence that supports the recommendations. The decision on whether to follow the treatment suggestions included in the prompt remained with the clinician. Control practices did not get any electronic prompts. The EHR database was used to measure the rate of antibiotic prescribing in intervention and control practices. Once the results have been analysed, it can be evaluated whether simple flagging procedures could be helpful in reducing antibiotic prescribing or whether more complex interventions will be needed to reduce the over-prescribing of antibiotics.

Another example of policy evaluation concerns an analysis of potential cost savings of substitution of brand by generic medicines and of changing medicines within the same class (i.e., therapeutic substitution). It was shown in an EHR database study that generic and therapeutic substitution would lead to potential annual savings of approximately €87 million in the Netherlands. The therapeutic substitution in this study consisted of switching patients on atorvastatin, fluvastatin or rosuvastatin to either simvastatin or pravastatin. This study concluded that from an economic point of view, society could gain by substituting statin therapy, especially from therapeutic substitution. However, this substitution may not always concern medicines that have equal effects or an equal evidence base on benefits and risks.

6.8 Informing cost-effectiveness analyses

EHR data have been used to provide information for cost-effectiveness and risk-benefit models. One study evaluated the cost-effectiveness of selective COX-2 inhibitors. It used the EHR data to estimate absolute risks for the outcomes of interest and then combined these with RCT evidence on the relative effects of selective COX-2 inhibitors in preventing gastrointestinal bleeding. The study found that cost-effectiveness models that only used RCT data had substantially exaggerated the cost-effectiveness of selective COX-2 inhibitors as the absolute risks of gastrointestinal disease were considerably lower in actual clinical practice. These findings strongly support that the evidence in health technology assessment consider the external validity of the information used rather than depending on data from authorization RCTs.
6.9 Other areas of use

EHR databases could also be used for measuring performance of clinicians and the auditing of their performance. However, it may prudent to separate research and audit activities. Access to EHR records for research purposes is often controlled by the clinicians with researchers dependent on clinicians for data access, validation of the EHR records and recruitment into prospective studies. Furthermore, EHR databases could be linked to registries that prospectively collect information on patients with a certain disease or using specific medicines. EHR databases may also be used to complement and enhance the results of RCTs.41 Potentially eligible RCT participants may be identified using the EHR databases and RCT participants could be followed long-term for major clinical outcomes. Natural language processing of electronically recorded notes of clinicians may allow better capture of the clinical information in this free text.

7. Integrating different EHR databases

Increasingly there is a need to perform studies on harms and/or benefits of medicines across different EHR systems and across different countries mainly for reasons of the need for a larger sample size. Evaluations of rare adverse events, comparisons of individual products or heterogeneity of drug effect in different subgroups of patient often cannot be done in a single database. The health care systems in most countries consist of multiple health care providers who often use different systems to store data (either paper or electronic). Furthermore, physicians often record data differently and inconsistently (both on paper and electronically). In order to analyse EHR from different countries and sources, various international initiatives using different approaches are currently ongoing. One approach focuses on IT aspects with the aim to develop EHR systems that are interoperable and allow the seamless transfer of data.42,43 This approach requires extensive redesigns of the IT systems. An alternative approach is to maintain the EHR data structure as collected by the health professionals but develop common protocols with similar research questions across databases adapting the operational definitions to each individual EHR database. This model is currently used by the Innovative Medicines Initiative PROTECT project.44 The OMOP initiative in the USA integrates all EHR data into a central research database according to a common data model.45 The fourth approach to dealing with heterogeneous EHR databases concerns a distributed model in which basic analyses are run on federated datasets followed by central pooling of results. The EU-ADR project uses this approach.46 Another approach is being followed by the Canadian CNODES initiative. In this initiative common protocols have been developed to study various drug-adverse event associations, but data are analysed locally in each province using multidimensional propensity scores to adjust for confounding and finally pool results through meta-analyses.47

Each of these approaches has advantages and disadvantages and in the coming years it will become clearer which approach may be the more successful. The IT redesign is clearly the most ambitious approach with the aim to have EHR systems that provide for systematic diagnoses using decision support systems, have uniform and standardised recording of clinical data and allow for seamless transfer of data between different health care providers. The ideal system for RCTs would be to build the case report form within the EHR so that data that have already been collected previously (in a standardised manner by fully trained
Update on 2004 Background Paper, BP 8.4 Use of clinical data

staff) could be imported seamlessly and immediately into it. While this may be ideal for research purposes, the development of large and expensive EHR systems has not unequivocally been successful, with several substantial failures and few successes. At a recent meeting at the USA Institute of Medicine (discussing large simple RCTs with simple recruitment and follow-up procedures), Michael Lauer of the National Institutes of Health advocated a willingness to experiment: emerging technologies should be embedded into existing projects and be allowed to fail often but inexpensively in smaller experiments. A stepwise approach to learning what works could be useful for expanding research with EHR data as long as lessons are captured and shared.

8. Ethical aspects and guidelines

Research access to EHR databases is typically restricted to data that are anonymised and do not contain patient identifiers such as names and addresses. Re-identification is, however, theoretically possible for an individual with an e.g. extremely rare condition or characteristic pattern of prescription dates. Data protection and security is thus of critical importance for researchers that use EHR databases. Staff training and standard procedures but also skills and attitudes of staff are important to treat data with appropriate care. Regular audits by external experts have been found to be very useful as it helps to maintain a culture of continuous improvement. This example from publishing audit findings and overall system of data security should be followed by other EHR databases.

The informed consent requirements for research use have been widely debated. In many countries, anonymised EHR data do not require informed consent of the patients. Some EHR databases use an opt-out system in which patients can refuse their data to be transmitted to the research database. Other EHR databases require an opt-in system in which patients have to provide consent to research use. A recent evaluation of patients approached for informed consent to use their medical records found significant differences between participants and non-participants. The authors of this study concluded that an opt-in system of consent may threaten the validity of results from observational studies. Clinical interventions need to be monitored and evaluated in order to identify opportunities for improvements. Without data, such activities would be impossible and harmful interventions could go unnoticed.

The models of ownership vary greatly between EHR databases. Ownership varies from governments, universities, independent organisations to commercial companies. The requirements for data access for research also vary, ranging from no external access to access after protocol approval. One of the concerns expressed by patients relate to sharing of EHR data with commercial companies. There has been a clear movement towards open access to research which could minimise any effects of conflict of interest. The Royal Society in the United Kingdom recommended an open data culture and, where the data justify it, scientists should make them available in an appropriate data repository. While it would not be appropriate to put all EHR data on-line for open access, an open data culture would support a model in which researchers can access to EHR data following scientific review of the protocol that is done fully independently of the owners of the EHR database. Patients want clear information about the process and implication of using EHR data. Transparency of access requirements would support this.
Registrations of the study prior to the start of the analyses and external access to protocols after completion of the analyses have been advocated strongly for RCTs. Access to research protocols may be even more important with research that uses EHR data: there are now several examples of studies that reached opposite conclusions when the same EHR database was used. One example concerns discrepant results concerning the possible effects of diabetes medication. Two studies recently evaluated this association in the Clinical Practice Research Datalink between diabetes medication and cancer. One study concluded that the use of metformin was associated with a decreased risk of pancreatic cancer in women only, whereas use of sulfonylureas and of insulin was associated with an increased risk of pancreatic cancer. The second study, conducted independently, concluded that there was no evidence of either beneficial or adverse effects of diabetes medication on cancer risk. These two studies varied in the design (case-control versus inception cohort) and in the definition of exposure. One can easily vary results by e.g. excluding certain patient groups or varying the definition of exposure or case definition. Research that use EHR data can be based on strictly *a-priori* defined criteria or on data dredging and post-hoc changing of study definitions. There are now several examples of studies, within the same EHR database but with different protocols, that reached opposite conclusions. External access to protocols will ensure that deviations from the protocol are transparent and subjected to peer review.

Initiatives have been taken to develop guidelines for the conduct of observational research with EHR databases. An important example is that the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. This is a collaborative scientific network coordinated by the European Medicines Agency and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. Its goal is to further strengthen the post-authorization monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorization studies focusing on safety and on benefit-risk, using available expertise and research experience across Europe. For comparative effectiveness studies, guidelines have also been published on the state of the art approaches to frame research questions and report findings for these studies.

### 9. EHR databases and learning health care systems

A health care system that generates and applies the best evidence for collaborative health care choices of each patient and provider has been defined as a learning health care system. Such a system would continuously test interventions and collect data on the outcomes and then use these results to inform clinical practice. EHR databases are an emerging technology that can help to fulfil this promise. Low-cost and low-risk pragmatic RCTs within EHR databases should be conducted as a matter of routine in order to resolve uncertainties that clinicians face in daily life. Variability in clinical care between clinicians due to incomplete evidence should be addressed by conducting a RCT. Additionally, using EHR databases in an optimal fashion is of high importance for implementing adaptive licensing policies.

A recent analysis by John Ioannidis found that only one of the 24 blockbuster medicines (those with more than one billion US dollars in sales) had been studied in a RCT with more than 10 000 participants. This is an important deficiency because large RCTs are needed to evaluate effects on major clinical outcomes. For example, few of the RCTs with blockbuster...
medicines included death as an outcome, so we currently do not know whether these widely used medicines may increase mortality due to side-effects. Five of the blockbuster medicines included in the study by Ioannidis are used long-term to treat patients with mental-health problems but the use by millions of patients is based on RCTs of short-term duration (three to four months) enrolling only a few hundred patients. Simple pragmatic RCTs that use EHR data could address these uncertainties at low cost; patients would be randomised after consent and the EHRs would be used to record death (or other major clinical outcomes) unobtrusively. A standard RCT with 20,000 patients can cost over €350 million, while a simple pragmatic RCT within an EHR database would cost €7 million. As outlined in a recent article about the continuously rising costs for RCTs, “reducing the costs of trials is absolutely crucial for the public good”.

Adaptive licensing of medicines is being considered as a model that allows step-wise authorization of medicines, with iterative phases of data gathering and regulatory evaluation. Initial smaller RCTs are followed by larger ones and authorization approval by the regulatory authorities is reconsidered repeatedly with fewer licensing conditions being imposed over time in case of successful studies. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. EHR databases can play a critical role in implementing adaptive licensing in a cost-effective manner. More limited pre-authorization studies could be followed by larger simple RCTs that collect mortality rates and major clinical outcomes through the EHRs, and additional outcomes through study-specific case report forms. Participants in these pragmatic RCTs would be randomised between the novel intervention and the standard of care. The ideal would be that the earlier studies would be done in specialist centres in carefully selected patients but over time a broader spectrum of clinicians and patients would be involved. Similarly, the earlier studies would implement rigid monitoring of trial participants while the later RCTs in the broader populations would mimic the monitoring as would be routine. Such an approach could address the current gap between internal and external validity of RCTs. In order for this approach to work, the current regulatory framework will need to change. The concept of risk proportionality to research governance needs to be embraced fully, so that many more clinicians and patients are willing to participate in research. Currently, only a small minority of clinicians and patients participate in research, even when it concerns low risk pragmatic RCTs. In our ongoing simple pragmatic RCT comparing simvastatin and atorvastatin (two widely medicines), less than 10% of the clinicians were willing to participate and complete the numerous paper forms and training in how to prescribe a statin (which they have done already to hundreds of patients). The health care system needs RCT evidence to guide interventions but its practitioners currently seem unwilling to generate it. Adaptive licensing can only be a success if more clinicians and patients participate in simple RCTs with research governance proportional to the risks imposed by a RCT.
10. Identified gaps and recommendations for research

EHR databases permit unobtrusive long-term data collection on major clinical outcomes. With increasing computerisation of health care system, the quality and completeness of EHR data has been increasing over time. These databases provide an opportunity to integrate research and clinical care. But there remain several gaps related to the use of EHR databases for research and policy. To unlock the full value of EHR databases, investment is needed at the European level to create an efficient infrastructure for research and innovation. The development and appropriate use of EHR databases is essential, especially for the success of new policy initiatives such as adaptive licensing and various pricing schemes. Efforts to strengthen the capabilities of Europe in this area and to build on existing infrastructure are of key importance. Furthermore, from a public health perspective, data that are gathered as part of (publicly funded) health care practice should be available to a broad audience, if the data is of appropriate quality. The key activities to be supported are:

Establishment of a funded European Research Network for the conduct of comparative effectiveness studies
The United States Agency for Healthcare Research and Quality funds the development of the research infrastructure to identify new and emerging clinical interventions, review and synthesise current medical research, identify gaps between existing medical research and the needs of clinical practice, promote and generate new scientific evidence and analytic tools, train and develop clinical researchers, translate and disseminate research findings to diverse stakeholders and reach out to stakeholders via a citizens forum. In Europe, networks have been established and funded for the review and synthesis of the evidence on the effects of medicines and for the conduct of cost-effectiveness analyses and health technology assessments. However, there is currently no funded infrastructure across Europe to conduct comparative effectiveness studies and generate the evidence that may be needed to inform health technology assessments. Such a network could build on existing strengths and fund the development of the research infrastructure. A European network could strengthen the collaborations within Europe and help to build on the unique strengths in Europe of EHR databases.

A focus on systematic measurement of data quality
EHRs are increasingly being used for research and public health purposes. The content of EHR databases varies greatly as information is being collected for different reasons and using different software and coding systems. Also, information in EHR databases can change substantially over time. As an example of temporal changes, the Quality and Outcomes Framework introduced in England in 2004 resulted in a substantive increase of the data recorded in the EHR databases as clinicians were incentivised to record information. The traditional methods of measuring data quality consisted of comparing the paper charts with the electronically recorded information. This model is increasingly less useful as more and more clinics are using paper-less record systems. Given this multitude of EHR databases, their varying content and possibility of changes in recording over time, there is a need to develop and implement statistical models of data quality. The ideal would be to have models that regularly evaluate the quality of the EHR database for the information that is at a minimum required for a certain study.
Development of methods to predict long-term risks in EHR databases

A multitude of advanced statistical models, such as neural networks and artificial intelligence models, are being applied to large datasets including EHR databases. The objective of these analyses is to improve the prediction of risks of adverse outcomes. But the methods of comparing different statistical models in risk prediction are not yet fully developed. The traditional approach of dividing a dataset into a development and testing dataset may be less applicable to very large databases as one would get statistically similar results. Risk prediction models typically use multiple imputations to deal with data that are not recorded or measured. The underlying assumptions of this technique are typically not met in EHR databases as recording of information (and visits to health care system) are determined by the health status of the patient. The further development of risk prediction with EHR databases can support clinicians in identifying patients who require medical review.

Creation of a European resource to make uncertainties in routinely used interventions explicit and to help prioritize new research

The priorities for research on interventions already used in the health care should ideally be determined by clinicians and patients, rather than by the funders. Patients and the public have a right to expect that research funders, researchers and health care professionals are aware of uncertainties about the effects of treatments. In the United Kingdom, a Database of Uncertainties about the Effects of Treatments publishes treatment uncertainties from patients, carers, clinicians, and from research recommendations, covering a wide variety of health problems. Several sources are used to identify uncertainties about the effects of treatments, including the patients', carers' and clinicians' questions about the effects of treatment, research recommendations in reports of systematic reviews and ongoing research. A European resource on treatment uncertainties could help to set priorities for public health funding in Europe.

Addressing these research questions would ensure that progress is made on the structural, technical and legal/ethical aspects and help to unlock the full potential value in EHR databases. The European pharmaceutical industry, regulators, pricing and reimbursement authorities and patients would all benefit from having interoperable, quality-assured EHR databases available and accessible. Such a pan-European resource would be a major competitive advantage for Europe.

11. Recommendations for policy

Introduction of risk proportionality in research governance for low risk RCTs

The pre-amble of the 2012 proposed revision of the Trial Directive acknowledges the negative effects of the current legislation. One of the proposed changes in the European Trial Directive concerns the inclusion of low risk RCTs, which could include simple pragmatic RCTs that use EHR databases. It defines low-risk RCTs to concern “authorised medicinal products, used in accordance with the terms of the marketing authorization or their use is a standard treatment and the additional diagnostic or monitoring procedures do not pose more than minimal
additional risk or burden to the safety of the subjects...”. Unfortunately, this very reasonable definition may not achieve the important need for simplification and risk proportionality in research governance. We must not continue on the current path of ever increasing complexity and costs of RCTs. Risk proportionality is essential in the research governance of RCTs and this should be made explicit in the legislation to facilitate research that aims to improve medical practice.

Data privacy and research use of EHR databases

There is considerable debate about whether (pseudo)anonymised health care data should be made available for research. Recently, the European Parliament’s rapporteur on the Data Protection Regulation published a draft report with potentially significant consequences for research using health data. The rapporteur’s report stated that “processing of sensitive data for historical, statistical and scientific research purposes is not as urgent or compelling as public health or social protection.” The rapporteur’s report proposed 350 amendments to the Data Protection Regulation. It stated that pseudo(anonymised) data could be used without consent, but only in cases of “exceptionally high public interest” such as bioterrorism. Many people have expressed concerns on the potential negative impact of these amendments to the European Data Protection Regulation to delivering high quality, patient-centred health care and conducting effective clinical and public health research, including the European Federation of Pharmaceutical Industries and Associations and the EU Biobanking and Biomolecular Research Infrastructures.

The right of data privacy is indeed very important and high data standards of data protection are essential for any EHR database. The critical question is whether the right of data privacy trumps all other rights and duties or whether a balance is possible between different considerations. There is also the right of patients to receive proper treatments and the duty of the health care system to, for example, monitor treatments for effectiveness and safety and be cost-effective. The discussion around data privacy should also consider these other rights and duties. Furthermore, it should also consider how to minimise the risk of breaches of data privacy with appropriate data security procedures. An opt-out system, in which patients can refuse to have their data used for research and health care evaluations, is one approach in order to achieve a balance between the rights of data privacy and the duties of the health care system to provide effective interventions in a cost-efficient manner. If it would be logistically difficult to implement such an system, (pseudo-)anonymisation and strict security standards should substantially minimise the risk of breaches of data privacy. A survey of over 1 000 adults found that 97% agreed with the statement that the health care system “has a duty to determine the safety and effectiveness of the drugs its doctors prescribe”. This topic, and the merit of the different approaches, is also being discussed in new European legislation.

Transparency in data security standards

Data protection and security standards are of critical importance to EHR databases. Regular audits by external experts and publication of the results could lead to maintain a culture of continuous improvement. EHR databases need to be accountable for the use of the EHR data, including reviews of the data use by licensees of the database.
Transparency in the research use of EHR data

Research use of the EHR database should follow highest scientific and ethical standards. There is considerable controversy whether all observational studies need to be registered and full methods and results published. This approach of full disclosure is being advocated strongly for RCTs. A recent workshop on the need for registration of observational studies concluded that this would increase and ethical aspects of observational results. This registration should cover the study protocol and any amendments, the a priori defined hypotheses and study results. However, these recommendations have not been not accepted universally. Arguments against the registration of observational studies include the possible bureaucracy of registration, the timing of a research hypothesis (whether before or after data collection) may be irrelevant to its validity, the potential “transparency” of such registered information could easily be clouded by the complexity of assembling the information and that hypothesis-free exploration may yield new hypotheses. However, the large amount of information in EHR database can allow unscrupulous researchers to cherry-pick the results and publish the findings in the highest impact journals. An analysis of hip fracture risk with statin use found that the range of results varied from highly statistically significant to non-significant associations. The results of this study varied substantially by changing the exposure definitions, the method of age matching and the selection of risk factors in the regression analysis. While data mining and the generation of hypotheses through careful review of the data are scientifically important, there remains the possibility that unscrupulous researchers present post-hoc data dredging as a scientific exercise. Transparency of use of EHR data and a simple model for registration of research protocols (at the time of publication) should be welcomed as researchers should be accountable for the use of the data. Deviations from a protocol may occur and post-hoc analyses may provide important results but researchers should be able to explain these and be transparent.

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