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

See Background Paper 8.4 (BP8_4Data.pdf)

The costs of pharmaceutical R&D are high, with clinical trials being a major component of these development costs. At the same time, 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. Data obtained from health information systems can be used to support innovation, detect safety problems and assess the real-world effectiveness of medicines. These data are now more widely available than ever before and offer new opportunities for research and health systems development. 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.”\(^1\) Although progress has been made since then the potential is still largely unfulfilled.

Medicine use in clinical practice frequently differs widely from the (pre-approval) clinical trial settings. Clinical trials are typically conducted according to a well-defined set of regulations, guidelines and ethical criteria. As a result, strict inclusion/exclusion criteria exist, based on age, gender, comorbidity and geographical location. This contrasts with medicine use in the ‘real world’. Here, the patient mix may differ greatly from the clinical trial population. For example, the main trials for selective COX-2 inhibitors such as rofecoxib and celecoxib were on patients with severe osteoarthritis or rheumatoid arthritis and aimed at long-term use (six to nine months). However, the majority of patients who were prescribed these medicines in clinical practice did not have these diseases. In addition, the duration of use was shorter and the daily doses were about one-third of those used in the clinical trial setting.\(^2\)

Meanwhile, various aspects that are not included in the trial setting play an important role in the real world. One of the key influences on real-life effectiveness is adherence and persistence. For example, in the pivotal trial of alendronate for treating osteoporosis, 89% of study participants were still using the medicine after three years.\(^3\) However, in a real life setting, after the same period only about 35% of patients were still using the medicine.\(^4\) These realities raise important questions about the external validity of trial results, and account for what is described as the gap between ‘efficacy’ (the trial effects of medicines) and ‘effectiveness’ (the real-world effects of medicines).
Potential value of electronic health records (EHRs)

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.” 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.

Historically, EHR databases have played a key role in evaluating drug safety. A more recent development in this area is the increasing use of EHR databases for pharmacogenetic research. This could, for instance, assist in the development of a stratified medicine approach by identifying populations at highest risk for adverse effects. EHR databases can also be used for finding novel relationships between diseases, re-evaluating medicine usage and discovering phenotype-genotype associations. As EHR databases and related methodology become more refined, this will be of increasing importance for drug discovery and development (e.g. by facilitating adaptive licensing and other approaches to speed up drug development). Adaptive licensing is being considered as a model that allows step-wise authorization of medicines, with iterative phases of data gathering and regulatory evaluation. More focused pre-authorization studies could be followed by larger point-of-care trials that collect outcomes which can be routinely obtained using EHRs.

EHR databases are routinely used to measure the uptake and outcomes of medicine use. In various studies using different data sources and in different health care settings, the lost opportunity from non-adherence is well described (see also alendronate example described above). EHRs can help identify where problems are located and thus can provide leads for innovation (e.g. for new dosing forms and formulations) and can fuel powerful tools to predict long-term risk of disease. An example is the QRISK score, which predicts the 10-year risk of cardiovascular disease. Risk scores such as these can be implemented in treatment guidelines (as is done in the United Kingdom for statins).

Another major potential of EHR databases lies in facilitating research in the area of comparative effectiveness or relative effectiveness, 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
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*practice.*" EHR methods can provide valuable and extremely cost-effective tools to assess relative effectiveness. A properly performed trial using real-life data may provide a far better estimate of actual effectiveness than efficacy derived from pre-approval clinical trials, especially when these trials lack statistical power (e.g. due to low sample size). For example, in such a trial using real-life data patients would be recruited at the point of care, randomized among routinely available interventions, and followed up using the EHR data. An illustration is the randomization of patients between atorvastatin or simvastatin with monitoring of major clinical outcomes with the EHR. Data from such studies could be used as the basis for value-based pricing.

Also, the impact of pharmaceutical policy interventions and prioritization of research needs can be studied in detail using EHRs. An example of policy evaluation is the measurement of the impact of a discontinuation of reimbursement of oral contraceptives. An example of priority setting would be off-label medicines use in children. In all these areas EHRs provide the potential to test policy interventions and to identify or fill knowledge gaps about how medicines are used in clinical practice. Therefore, effective models for HER data-use and sharing would also facilitate R&D within an ‘open innovation’ paradigm, which is one of a number of new business models being proposed for the pharmaceutical industry.

**Challenges**

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. In order to develop EHRs to their full potential, three critical aspects have to be taken into consideration:

- **Structural** (e.g. ‘ownership of data’, incentives for health care professionals to participate and collaborate).
- **Technical** (e.g. quality of data, IT, methods of record linkage).
- **Legal/ethical** (e.g. data confidentiality, privacy protection).

There are currently over 300 EHR databases in 45 countries. The content of these EHR databases varies greatly as information is being collected for different reasons and using different software and coding systems. In this report, five major issues that need to be resolved have been highlighted in light of the three aspects mentioned above:

- Not all EHR databases may be of sufficient quality for research. Three dimensions of data quality may be fundamental and need to be addressed: correctness (are the data valid?); completeness (is the ‘whole truth’ known about a patient? Can the information captured be used in different systems?); and currency (what is the time lag between an ‘event’ and the update of the EHR?). The conventional answer to the challenge of completeness is to ensure interoperability. However, this is extremely hard to do in practice. Many countries have spent substantial resources on this, with only limited success.
Evaluations of rare adverse events, comparisons of individual products or the heterogeneity of drug effects in different sub-groups of patients often cannot be done in a single database. Therefore, there is a need to perform studies across different EHR systems and across different countries and find ways to integrate the different datasets to generate results.

Another challenge for observation research is “confounding.” Confounding means that observed differences between comparison groups are not caused by the exposure of interest but by unevenly distributed risk factors. Confounding can play an important role, especially when comparing interventions.

Research that uses 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 subject to peer review.

The right of data privacy is crucial and high standards of data protection are essential for any EHR database. Analyses using EHR databases often use anonymized data. In many countries, anonymized EHR data do not require the informed consent of the patients. Some EHR databases use an opt-out system in which patients can refuse that their data is transmitted to the research database. Other EHR databases require an opt-in system in which patients have to provide consent to research use. This topic, and the merit of the different approaches, is also being discussed in new European legislation. The critical question is whether the right of data privacy trumps all other rights and duties or whether there is a balance between different considerations. For example, in an adaptive licensing system the balance between the individual’s right to ‘control’ the use of his or her personal information and public health may put more emphasis on the latter.

Research recommendations

To unlock the full value of EHR databases, investment is needed at the European level to create a good 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:

- **Establish a funded European research network for comparative effectiveness and health policy evaluation:** In contrast to the situation in the United States, there is no funded European research network on comparative effectiveness and health care policy evaluations. Such a network could build on existing strengths and fund the development of the research infrastructure. The key focus for this
would be methodology development, and collectively addressing the challenges described above (data quality, integration or at least interoperability of datasets, confounding, protocol publication and privacy). This network could also help to facilitate a dialogue about the availability and use of real-life data.

- **Focus on the development of new statistical models for the systematic measurement of data quality:** Information in EHR databases can change substantially over time. In view of the multitude of EHR databases, their varying content and possible changes in recording methods 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 through the use of EHR databases:** A multitude of advanced statistical 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 for risk prediction are not yet fully developed. The further development of risk prediction with EHR databases can support clinicians in identifying patients who require medical review.

- **Create a European database to make explicit the uncertainties in routinely used interventions and to help prioritize new research:** For appropriate priority setting, researchers and health care professionals need to be aware of uncertainties about the effects of treatments. In the United Kingdom, a Database of Uncertainties about the Effects of Treatments (United Kingdom DUETs) 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 questions from the patients, carers and clinicians about the effects of treatment, research recommendations in reports of systematic reviews and ongoing research.16

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.

**References**


14 ISPOR. Available at: [http://www.ispor.org/intl_databases](http://www.ispor.org/intl_databases).
