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CURRENT OPINION

Nordic Health Registers as a Source for Value-Based Evidence

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Abstract The study and approval of new drugs for use in humans has historically been based on three elements: safety, efficacy and quality. Towards the end of last century, different biomarkers and surrogate endpoints were considered appropriate for documenting new treatments. Most of our therapeutic progress during this period was developed within that viewpoint, and has been implemented in healthcare with great success. However, when it became harder and harder to demonstrate superiority of new drugs over existing therapies, combined with increasing healthcare costs, new needs came to the surface. The validity or appropriateness of surrogate endpoints was challenged, and the requirement to demonstrate value to society, in addition to safety, efficacy and quality, has become the new standard. A value proposition for new drugs will include focus on hard endpoints such as survival, but also longitudinal data on the patient's life and the societal impact of their disease. In the Nordic countries, and also in the UK and other European countries, there is an increasing interest in using health and quality registers to establish this new type of evidence. A few examples out of the vast number of registers are presented, to illustrate their potential as a valuable source of knowledge.

Key Points

Value-based evidence will become a key criteria for assessing new therapies

Health registers in the Nordic countries are useful sources of such evidence

Several studies are now published in which health registers are used to provide value-based evidence

1 Introduction

In the last 20 years of the last century, we experienced great progress in the treatment of major disease areas such as infectious diseases, cardiovascular disorders, and respiratory, metabolic, gastrointestinal, and some neurological diseases. Through the traditional track of phase I, II and III trials, equality with, or superiority over, existing therapies or placebo was documented by surrogate parameters. These could be biomarkers of different types or evaluations such as blood pressure, spirometry, blood glucose, etc. The development of secondary prophylaxis against cardiovascular diseases should show the rise of a new type of assessment for new drugs. Effect on blood pressure or effect on blood cholesterol was no longer adequate for entering the market; effect on long-term disease and survival became the new hard endpoints. As such, a fourth hurdle to market access and the need to demonstrate value to society was established.

However, this need to document value-based evidence has several aspects. Huge progress in the treatment of many of the widespread diseases had made it difficult to show

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superiority of new drugs over existing ones. The cost of development of new drugs escalated, attrition in the industry was high, and the hope of new blockbusters seemed to fade away. Governments struggled with an increasing health gap; the difference between possibilities or expectation and affordability was increasing, and the existing health cost model was no longer sustainable.

This situation has caused the industry to revitalise their strategies and ways of working, and society has to request and consider new ways of assessing new therapies.

The pharmaceutical industry, and in particular "Big Pharma", struggles with their complex research and development (R&D) organisation, high attrition and the need to enter new global markets. In addition, the traditional phase I–III process has been the textbook of their R&D staff, while the need for more societal understanding and knowledge of building good value propositions may have lagged a bit behind.

We face a situation where access to new medicines is delayed. Traditional phase I–III studies have failed to show adequate value, and we have not yet found a solution to the dilemma of providing value to the patient versus value to society. The way forward is to build a platform to demonstrate value, in addition to the safety, efficacy and quality shown by phase I–III studies. This late-phase evidence generation is an emerging exercise. Although we have the science and tools available, we lack a uniform process for defining a sustainable value proposition for new drugs.

2 New Data Required

In society we see increased demands on quality and knowledge. Patients and the public in general expect more information and involvement. In the healthcare sector we see proposals to implement more quality metrics and certification, and algorithms and procedures are established across hospital boundaries.

We need to know how many people will recieve a given diagnosis every year. And, among all treatments available, which treatment gives the best efficacy from a societal view? Do some hospitals, or some countries, have better results than others? In each country, healthcare services establish key quality indicators. We need to know more about causality, and how to prevent disease and find new treatments. And, as before, but more and more critical, we need to know if unexpected events will occur, and have more precise information about risk factors.

Odd Aalen [1] has proposed new ways of understanding treatment effects. Survival and event history have been the mainstay in modern clinical research, while longitudinal data are often ignored, even if collected as part of the clinical study. Therefore, Aalen suggested bridging the gap between survival analyses and longitudinal data. However, these longer-term life history data are very complex, and the standard statistical methods fall short in analysing them.

3 Health Registers as Source of New Data

Health registers could be a unique source of knowledge. They contain information collected from different places and parts of the healthcare sector, and are defined as registers or catalogues where health information is systematically stored in a way that makes it retrievable at the individual patient level. Data can be analysed by groups, either by diagnosis, age or population, etc. That means they can be treatment-oriented, and can be used for actions to prevent, diagnose, treat or support health and rehabilitation related to the patient.

Such registers can be used for basic and health outcomes research, and for surveillance of chronic diseases. But they can, and should, also be used for phase IIIb or IV studies; they could then, in full context, be a valuable element in what we often refer to as late-phase research. Health registers are mainly placed within the healthcare or governmental sector.

The Nordic countries have particular potential for this type of value-based evidence as they established and developed registers very early, and they have a population with limited mobility. Although some differences exist, they have many similar health registers, which can be used in combination. Many of these health registers are based on mandatory reporting by regulation or law. There is no general informed consent, and data include each person's unique identification with birth date and gender and person-specific figures. Across the Nordic countries, there are several hundred different health and quality registers.

Great attention is now paid to the large cardiovascular registers such as the Danish Heart Register, the Myocardial Ischemia National Audit Project (MINAP) in the UK, and the Uppsala-based Swedeheart, which is a collaboration using several Swedish cardiovascular registers. Swedeheart has recently published the results of using a health register to perform a multicentre, randomised controlled clinical trial in 7,244 patients [the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial] [2]. Its aim was to study the clinical effect of thrombus aspiration before primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. Using this methodology, the research group could use data collected in the normal clinical setting, and run in parallel with clinical practice.

Another source of potentially valuable information are the biobanks. These can be quite diversified, from old repositories of pathology specimens as paraffin blocks to

the types of biobanks established during and after the human genome race to collect genetic data in the search for new biomarkers and pharmacogenetic knowledge. However, an added advantage of many biobanks is that they may be linked to, or supplemented by, longitudinal life history data, making them a potential diamond in the rough. HUNT (the Nord-Trøndelag health study)—a longitudinal population health study in Norway—is an example of such a comprehensive biobank [3]. HUNT is one of the largest health studies ever performed. It is a unique database of personal and family medical histories collected during three intensive studies, the first performed in 1984. It covers several generations, and part of the population has given data to all three studies, which makes the life history of the databank quite unique.

The influenza A (H1N1) pandemic in 2009 put healthcare providers and the industry in a dilemma. There was an immediate need for a vaccine, and for a recommendation to implement mass vaccination. A vaccine was developed in a fast-track way, with all basic safety measures taken. However, there were critics in society. In some countries, an increase in reported cases of narcolepsy was observed, and there were anecdotal reports regarding the risk of fetal death. Very soon, healthcare providers were asked for a valid explanation and scientific assessment of these risks, and only use of health registers could give timely and appropriate answers. Only a few years after the pandemic, studies showed an increased number of narcolepsy cases in the vaccinated population, although causality has not been established [4, 5]. Researchers from the Norwegian Institute of Public Health linked information on women of reproductive age to various national health registers [6]. They found that pandemic influenza virus infection in pregnancy was associated with an increased risk of fetal death, but vaccination during pregnancy reduced the risk of an influenza diagnosis. Accordingly, vaccination itself was not associated with increased fetal mortality, and may rather have reduced the risk of influenza-related fetal death during the pandemic. This knowledge was made possible by using all applicable registers, and combining them to answer a key health problem.

The examples mentioned—the TASTE trial and the pandemic vaccine pharmacovigilance study—are only two of many recent reports where new important evidence has been provided using this new methodology.

4 How to Collect Data from Health Registers and Biobanks

The examples mentioned may seem different from examples relevant for the study of new drugs or therapies. To some degree this is correct, but given the fact that a value proposition is made early in a clinical development plan, life history data and use of health registers should be acknowledged by product launch, or before. When Merck obtained market authorisation for their cervical cancer vaccine Gardasil®, the US FDA stated that a follow-up safety study should be done using the Nordic cancer registers [7].

There are several hurdles to overcome before we can fully exploit the potential of health registers. This is a new way of thinking. As previously mentioned, traditional medical statistics do not always grasp the complexity of these data. And there is a lack of competency in the industry, which is locked up in their traditional phase I–III and good clinical practice pigeonhole. Also, with regards to health registers, we see a very fragmented picture with many players. The registers often have an old-fashioned infrastructure and complicated handling of cases. There is no or difficult system interoperability, and electronic access is a grey area. The legal framework is complicated and insufficient, and we can easily get into debates and considerations about a potential threat to personal integrity. Some key questions should be addressed regarding the ownership of, and access to, these data. Questions regarding access to the data include who can use the data, and who should allow the use of the data.

The next stage that needs to be established is some kind of strategy for using this new type of data. For the development of new drugs, key evidence gap analyses must be done, and this should be part of the clinical development plan—all from phase I. What evidence is needed should be defined, and the process should be implemented in guidelines and regulations. We need to establish systems for accessing registers, and new partnerships need to be made.

The legislative framework also needs to be established. Both in the USA and the EU we see that this is now on the agenda. The FDA has invested US$2.5 billion to see how health registers can be used to evaluate new treatments, and the European Medicines Agency (EMA) has also started to assess this. It is of paramount importance that personal integrity and data protection are well covered. Site system incompatibility or limitations may be changed in order to make the data accessible. Therefore, security of information technology (IT) should be a priority.

If health register data is to be implemented in a development plan for a new therapy, this should occur in the late phase. From the perspective of conditional approval and value-based pricing, such research may be crucial, and neither industry nor regulators should hesitate to establish good procedures and guidelines.

5 Need for New Partnerships

The use of health registers to create value-based evidence cannot be a task for the industry in isolation, nor for the

regulators, payors or governments. If we seriously expect new treatments to make use of this type of information, and at the same time want to reduce drug attrition in the industry and escalating costs, we should establish new public–private partnerships to pursue this opportunity. Such a partnership project has been initiated by the Innovative Medicines Initiative (IMI). The EHR4CR (European Health Registers for Clinical Research) project is presented as a sustainable business model for using electronic health record (EHR) data for research purposes [8]. Swedeheart is, as previously mentioned, a collaboration of different Swedish health registers, which is based in the Uppsala Clinical Research Center. It has been built up as a collaborative effort, and is an example of how new institutions or entities are needed to provide future new evidence. More collaborative research and collaborative funding should take place in order to meet patients' need for safe and effective drugs to be available for everyone, regardless of economic, social or geographic background.

6 Concluding Comments

The arguments for the use of more register-based late-phase studies are that they are relatively inexpensive to conduct, involving large numbers of study subjects is possible, follow-up is easy, and no active recruitment of study subjects is required. These are real-life studies, with no bias due to artificial study design. The health and quality registers are designed for surveillance and research, and accordingly maintain complete and relevant data. Furthermore, it is possible to link different registers within nations and across different countries. Several reports have now been published that demonstrate the usefulness of registers for this purpose.

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