Science, Strategy, Execution

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FFT - Food for Thought

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Today's topic:

Artificial intelligence in clinical development

Hypothesis:

Big Data and Artificial Intelligence (AI) will make drug development more accurate, faster and more cost effective in a near future, transform the business model of the pharmaceutical industry as much as the medical profession, and lead to better treatment outcomes faster and at less cost for society.

Relevance:

We see already today that AI-supported use of available real-world data informs decisions in drug development and is even used for regulatory approval or line extension in certain cases. This trend is accelerating, with ever more data becoming available and accessible, and competitive and cost pressure increasing in the pharmaceutical world. We are likely to witness a profound change in the business model of the industry and the medical profession and may face optimistic outcomes for patients, society and the industry.

The world as we know it

To show the benefit of a medical intervention, comparison with non-intervention is key. To gain regulatory approval, drugmakers must demonstrate this benefit in randomised clinical trials, comparing their drug with current standard of care. More and more, payers and health systems require a quantitative proof of benefit also to justify reimbursement and price of a novel treatment via health technology assessment (HTA) processes.

Comparator arms, while indispensable for generating evidence, also have their disadvantages:

- They increase the number of patients that need to be recruited to a trial significantly, adding costs and delaying the obtention of results. This is particularly true in diseases with a low incidence or prevalence, or where the costs of standard of care are high, oncology for instance.
- Up to half of patients in the clinical trial will not receive a potentially improved treatment over standard of care. In life threatening diseases, this represents a fundamental ethical dilemma.
- The results in comparator arms, especially in placebo-controlled trials, often differ from those observed in a real-world setting. The so-called placebo effect is a constant in medical history and particularly evident in therapeutic areas such as neurology or psychiatry. More than once, unusually favourable outcomes of placebo arm have led to missing a primary endpoint and hence to negative trials with all their consequences.

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Obtaining solid evidence with alternatives to comparator arms as we know them is desirable, and we see trends in that direction.

What is changing

The availability of large datasets ("big data") as well as the tools to analyse them ("artificial intelligence" and "machine learning") have made it possible to emulate comparator arms to a certain extent and create so-called "synthetic control arms" (SCA). Another approach is that of creating virtual patients, also known as "digital twins".

Regulators become increasingly open to the use of synthetic or digital controls under certain conditions. The US FDA approved Brineura® (cerliponase α; Biomarin) for the treatment of CLN2, a rare, inherited neurodegenerative disease. Due to the rarity of the disease, a randomised control arm was not an option; rather, data were taken from historical data of 42 matched "digital twins". More recently, Alecesna® (alectinib, Roche) was granted a line extension by EMA for ALK+ Non-small-cell lung cancer (NSCLC), based on comparison of virtual arms extracted from other alectinib studies as well as from studies with comparator ceritinib by matching patients in different datasets and showing a significant and relevant advantage in overall survival *in silico*.

In fact, regulators become proactive in fostering the use of those novel methods. The FDA's Oncology Center of Excellence has launched Project Switch. The objective of this project is to retrospectively create SCAs that match control arms from successful clinical trials. The FDA also sponsors research work from tech company Aetion and the Brigham and Women's Hospital to replicate or even predict digitally results of randomised clinical trials.

Another use of AI-based methods is to assess (and correct for) placebo effects in indications where this effect is known to be high and impacting results. Matching placebo controls to real-world data is used to factor out this effect and obtain more accurate results on a treatment's true effectiveness.

Where this is going

There is good reason to believe that digital or virtual control arms extracted from real-world data will become the standard in some therapeutic areas. Therapeutic areas with certain characteristics will be faster in adopting this:

- Indications with large, thoroughly curated data sets (including genomic data) such as oncology or haematology
- Indications with very low incidence or prevalence, where the recruitment of comparator arms is very difficult, such as rare diseases
- Indications where placebo control is difficult to assess, for example when the placebo effect is generally high and may influence the result negatively, such as neurology or psychiatry diseases

Other therapeutic areas will follow, where the economic incentive to reduce trial size and duration is high, but where large, high-quality datasets are not yet available. Efforts to create large datasets accessible to AI approaches are underway, notably in cardiovascular diseases. BigData@Heart is such an example of a joint project between the European Society of Cardiology, academic research groups and pharmaceutical manufacturers to create a big-data driven translational research platform. Funded by the European Union, this database is intended to improve both research and development processes in speeding up innovation and improving outcomes for individual patients.

Generally, AI will enable efficient clinical development of treatments for smaller and better defined populations and represent a major advancement in the pursuit of Personalised Medicine. Maybe it will drive the breakthrough for this concept in disease areas that are still considered "mass market", such as many cardiovascular diseases, and transform the management of these diseases

fundamentally. In therapeutic areas like solid tumours, the trend towards personalised medicine will be accelerated.

Ultimately, all this will affect the business model of the pharmaceutical industry. Target populations will shrink, narrowing the field for "blockbuster" or "anchor" drugs worth several billions on annual sales. At the same time, development time and investment per project will shrink as trials can be smaller, and expensive treatment under study conditions can be replaced in part by *in-silico* research. Also, upfront, at-risk investment in translational research or production of study drug will be less, reducing cost additionally and speeding up proof-of-concept decisions. Failure rate in later stage may also be significantly reduced, and with it the extremely high financial risk associated with investment in pharma and health technology projects.

Full development of their assets by startup companies will be more affordable, and pressure to rely on partnership with large corporations may become lower. Instead, we will see more close cooperation or even joint-venture type business models between biotechnology and IT companies arising.

Profound effects are also to be expected on the nature of the medical profession itself; specialists may need to rely much more on AI-based algorithms themselves when treating individual patients to be able to direct patients to the right treatment. Advanced diagnostic methods including genomic analysis and other "-omics" will become available and even standard in disease areas where they don't play a role at all today. We have seen how they transformed Oncology within a decade. On the other hand, clinical trials will be transformed but not replaced by *in-silico* development in an overseeable future. Too complex is the interaction between molecules, cells, tissues, and organs in a human body. The ultimate proof of clinical benefit will still require the test in patients.

It is hard to predict the extent to which this shift in how therapies are being developed and applied will improve outcomes for patients, speed up innovation and reduce overall healthcare costs for societies, but there is good reason to believe that we will see all three of these happen in a near future.

Exciting times ahead.

References:

Debunking Top 5 Myths about Digital Twins in Clinical Trials (appliedclinicaltrialsonline.com)
Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib (becarispublishing.com)
Transforming Clinical Trials with Real-World Evidence | BCG
Using Artificial Intelligence-based Methods to Address the Placebo Response in Clinical Trials - PubMed (nih.gov)
Big Data in Cardiovascular Disease | European Heart Journal | Oxford Academic (oup.com)