PEER REVIEWED

Personalised Medicine and Clinical Studies – The Attempt to Untie a Gordian Knot –

Introduction

Classical drug development is undoubtedly indication- and product-driven. Simply put, a preclinically developed substance is optimised for clinical application in an appropriate galenic preparation and, in the best case, brought to market maturity in various phases of clinical development.

The classical medicines of the western type, tried and tested and established, have recognisable disadvantages. With exceptions, these products usually only promise relief, acute illnesses turn into chronic diseases with sometimes lifelong necessary treatment. Moreover, clinical development is a lengthy process and often still fails in late phase III.

New therapeutic approaches promise targeted preclinical development, lower failure rates in the subsequent development steps and fewer adverse effects due to the target orientation.

Technical Approach

The trend towards personalised medicine or precision medicine towards targeted therapies is revolutionising drug development as we move from a blockbuster to a niche mentality. (Figure 1)

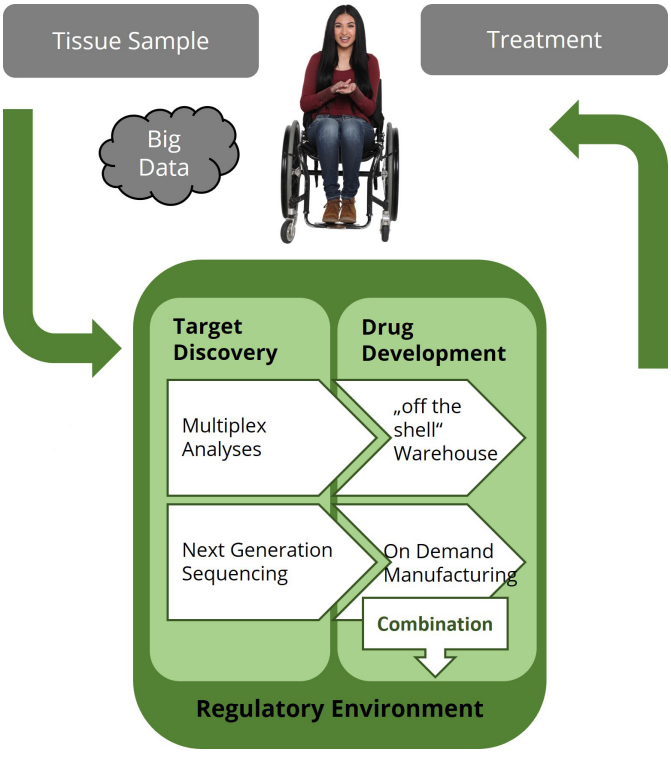

Figure 1

This development is driven by two strong trends, almost medical megatrends, molecular genetics-assisted diagnostics, and treatment + (Figure 2), and data analytics.[1]

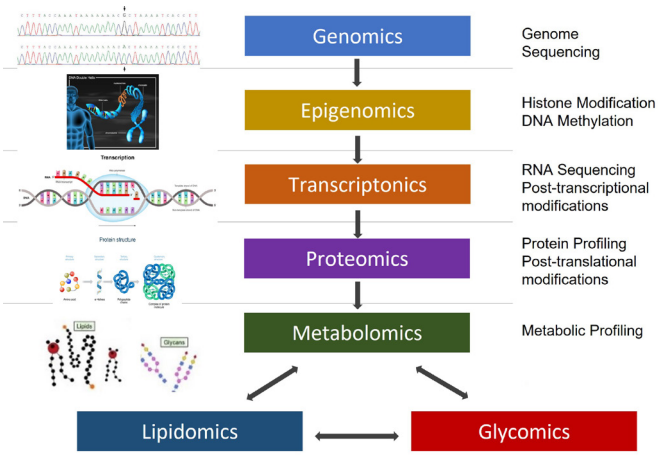

Figure 2[26]

Only evolutionary development into a holistic approach will unleash the full efficacy of personalised treatment strategies.[2]

1. Over the last two decades, the amount of data in the field of oncology has increased rapidly. For each individual patient, more and more data are being generated and stored. For example, in the European Innovative Medicines Initiative project OncoTrack, close to 1 terabyte (1,000 gigabytes) of data are produced per patient, which is equivalent to 250,000 photos or 6.5 million document pages. This increase in stored information was sparked and promoted by the digitalisation of medicine and technological advances, such as genome sequencing.

\+ The most promising scientific breakthroughsin medical research are only as good as the quality of the clinical operations that accompany them into the clinical setting.

Personalised medicine (PM) aims to harness a wave of 'omics' discoveries to tailor drug choices, dosages, and interventions to the biology of individual patients.[25]

Study Design

The population-determined protocols can generally pinpoint suitable treatments/interventions for individuals, but the emergence of artificial intelligence (AI) and digital medicine offers the potential to truly optimise patient outcomes.[3]

Strategies for vetting personalised medicines have been developed, in cancer contexts, and include 'basket,' 'umbrella' and adaptive – platform trials,[4,5,6,7] but the assumptions and measures described should be applicable to other medical specialties as well.

The complexity of clinical trial designs increases with the degree of product individualisation + + and the number of questions addressed[8] (Figure 3), which directly affects the trial design.

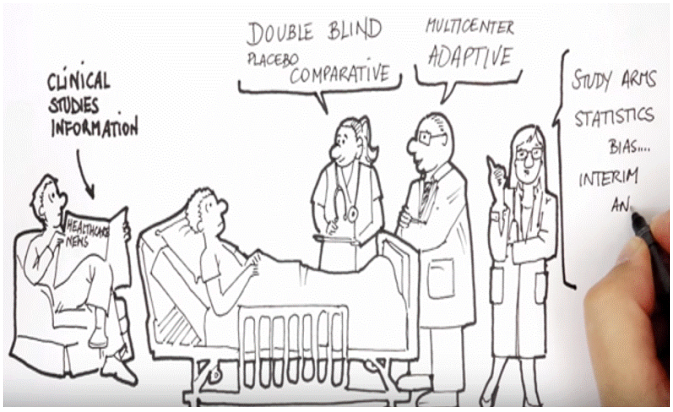

Figure 3

++ This means that the highest complexity is reached at N = 1. The extent to which a single patient in a clinical study allows statistically significant statements to be made about treatment due to the enormous amount of data is a matter of controversial debate but will not be dealt with further in this paper.

This shift in the conduct of clinical trials has its origins not only in the technologies described but also in the resulting different questions. The classic "intervention focused" clinical trials only ask the question "can this intervention offer benefit over current standards of care or placebo?", while the more "disease focused" platform trials look for the best intervention for a given disease.[9] (Figure 4)

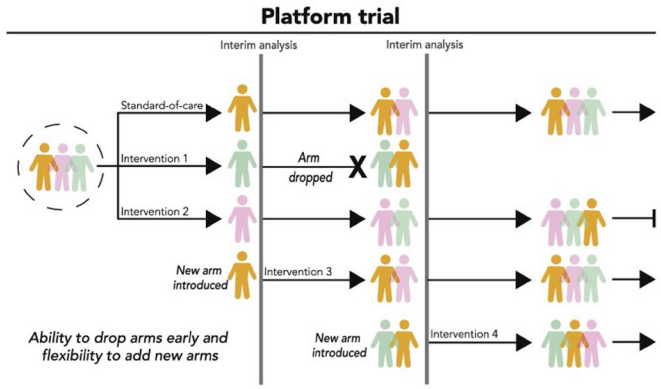

Figure 4

This study design offers many advantages but requires a differentiated approach to implementation. Currently, the FDA has published the Guidance for Industry "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics" in March 2022[10] and offers consultation support.

It is clear from the personalised target-oriented therapeutic approach that placebo-controlled studies are unlikely to occur for ethical reasons (although there may be justified exceptions).[11]

It seems that with this study concept, better and more precise planning can be made. With a larger product pipeline, resources can be better planned, and the allocation of funds optimised with a structured clinical development plan.

How to Decrease Costs and Increase Quality and Meaningfulness?

To gain the most benefit, they should discard the belief in the first-patient-in. The timing of the last-patient-out must become the criterion for success.[12]

Extend follow-up periods to learn more about e.g., vaccination, if needed.

NOTE: Follow-up periods may add scientific value, but the benefit for an individual patient is uncertain.[13]

Keep the number of involved sites and countries low, this will give you a better handling of the key indicators (see below). This is usually feasible because patient numbers are smaller, a large Phase III trial is rarely necessary, and the usual concerns of statistical error due to low or over-recruitment at a centre have less impact, but the skills needed to implement these complex protocols are critical to success.

Involve trained clinical researchers and back-ups. Contact and inform the medical doctors and staff regularly about forthcoming activities and keep them well trained in common clinical research issues also without direct study relationship. This will make starting the next trial faster and easier.

Pay attention to and use the key-success indicators performance, risk, safety and financial. Due to the protocol complexity and flexibility (adaptive), it is essential to establish a Data Monitoring and Safety Committee.[14]

Trial Management with Adaptive Protocols

Although the conduct of the study on the part of the sponsor as well as its representatives and trial sites are undoubtedly extremely important, there are hardly any practical guides or literature to be found on this.[15]

This is surprising because the operational conduct of a clinical trial is the most complex, also because many people are involved and need to be coordinated to achieve the common goal.

The prioritisation is sometimes very different from traditional protocols and almost similar to those used in rare disease trials.[16]

Table 1 shows an example of the increasing responsibility of the people involved in such projects.

Task	Conventional studies	Adaptive Design
Contact with authorities	*	***
Patient Retention	**	***
Contact with KOLs	*	***
Patient database	N/A	**
Market knowledge	*	*
Patient organisations	*	**
Project management	**	***
Clinical monitoring	*	***
Table is for illustrative purposes only		

* Less priority / responsibility
** usual implementation and responsibility
*** Very important / high responsibility

Table 2: Prioritisation at project level

It is therefore necessary to relieve the operational staff of routine tasks in order to allow more time for the important areas.

It may sound absurd, given the increasing responsibility in so-called clinical monitoring, to cut back on several sectors, especially with regard to the time-consuming on-site visits, but this is exactly what I strongly advise.

Firstly, more GCP-relevant responsibilities are being fulfilled by the trial centers, secondly, more and more data are being automatically transferred to study databases in anonymised form

for analysis (Figure 5), and thirdly, with these data volumes, classical clinical monitoring is simply no longer economically feasible.

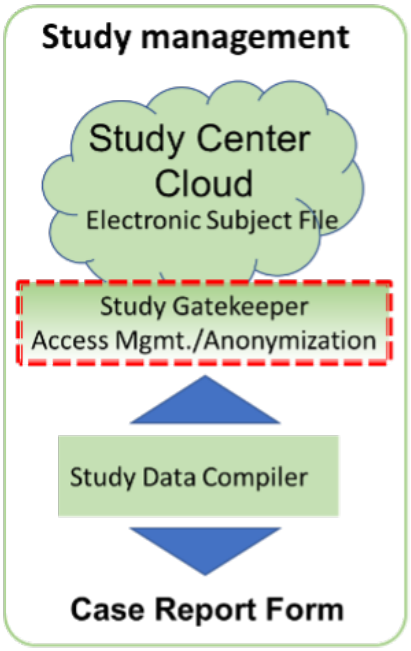

Figure 5

In any case, the new digital technologies will finally help the approach of centralised monitoring to make a breakthrough.[17,18,19]

This means that scientifically and medically well-trained staff will have enough time for safety-related topics and the management of the projects. This should have a significant qualitative added value.

The Health Care Industry – Ready for Digitisation?

The healthcare industry offers many opportunities to use the latest technologies. From pre-clinical research to solving complex problems at the molecular level using quantum computers,[20] the decentralised management of patient data in hospitals through cloud-based solutions and distributed-ledger-technologies that replace insecure warehousing solutions21), identification solutions in distribution management to drug tracking using blockchain,[22] as well as AI driven technologies in research projects are often based on learning algorithms (machine learning).[23] Not to forget the technologies we discussed earlier in this paper.

Admittedly, the pharmaceutical industry is only at the beginning of its digital development, but this is progressing rapidly and those who want to place competitive products in the future should escalate the organisational development.[24]

Conclusion

As translational medicine has evolved from a unilateral model to a bilateral model (Figure 6) with subsequent involvement of society,[28] the digital world is also changing.

This has a great impact on the "translation speed" from research to clinical reality and thus on the way clinical trials are conducted.

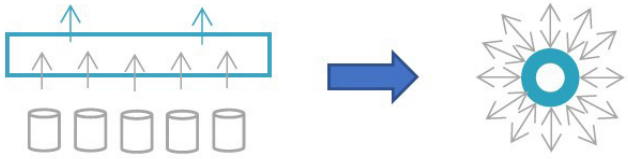

Figure 6

Finally, a small contribution to a possible development:

With the introduction of new technologies, e.g., in the prediction of the 3-dimensional protein structure from the one-dimensional amino acid sequence,[27] diseases and their causes can be better understood at the molecular level and therapy approaches can be optimised. The question arises: "At what threshold of precision are clinical studies still useful? In the not-too-distant future, will it only be necessary to validate the manufacturing processes or technologies as medical products?

Exciting times!

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