INNOVATIVE PROTOCOL DESIGNS IN EARLY PHASE CLINICAL DEVELOPMENT

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OVERVIEW

It is no secret that research and development (R&D) in the pharmaceutical and biotechnology sectors has often been characterized as slow and costly. Less than 1 in 10 new drugs reach the market and around 85% of potential drug therapies do not pass early clinical trials. These data suggest that increasing research and development (R&D) productivity and reducing costs could start with changes in early phase clinical development. With this in mind, the present whitepaper reviews some of the recent trends in protocol design and digitalization, as well key regulatory opportunities and challenges that those conducting clinical trials in Europe should consider.

INTRODUCTION

The costs of researching, developing and regulating a drug can be as high as $2.6 billion.\(^1\) It has been argued that drug developers are often losing promising products as a result of using development strategies based on outdated clinical trial designs. This assumption implies that alternative ways of developing new drug products must be implemented starting with the earliest phases of clinical trial. Developing and implementing new drug development models requires the participation of companies, regulators, academic institutions, governmental agencies, and patient advocacies. Rosenblatt et al.\(^2\) suggest several opportunities to improve clinical trials in terms of speed and costs by taking into consideration both protocol designs and contextual variables such as collaborations.

These opportunities include:

**Find new targets:** The Human Genome Project has provided thousands of drug targets that can be considered. A precompetitive effort to assess which targets are the most likely to provide positive results could increase the success rate of drug development.

**Use predictive toxicology and efficacy:** Approaches such as pathway-based systems biology and organ-on-a-chip could deliver more efficient and accurate predictions of safety and efficacy.

**Take advantage of existing drugs:** Products that have already been approved for another disease can sometimes be used to target a different condition. The discovery of diseases that were thought to be independent but are mechanistically related provides the opportunity to treat several diseases with a product that has already been approved or is in development.

**Use combination therapies:** The development of methods to identify combinations of drug candidates with increased efficacy and reduced safety risks could increase the effectiveness of individual therapies developed or in development. This can work with dedicated technology development, testing, and clinical-development frameworks.

**Use gene-based and cell-based therapies:** The emergence of powerful new gene-editing techniques such as CRISPR-Cas9 and the increasing flexibility of stem-cell...
technologies offer many opportunities to provide transformational therapies complementary to small-molecule and protein drugs.

**Value precompetitive collaboration:** More organized precompetitive collaborations involving companies, governments, and academic institutions can improve drug discovery, particularly in areas where substantial scientific background is missing. Examples of such developments include Accelerating Medicine Partnership³ and Alzheimer’s Disease Neuroimaging Initiative⁴.

**Develop qualified biomarkers:** There is a limited number of qualified biomarkers or combinations of them that can fasten the drug-development and regulatory process. As such, there is a clear need for a biomarker-qualification process. Achieving this requires a good understanding of the context of use and a consideration of the benefits and risks of the market, as well as an understanding of the type of evidence standards required to approve the biomarker for use in preclinical and clinical testing.

**Make use of real-world evidence (RWE):** It is now possible to obtain data concerning the clinical efficacy and safety of drugs from real-world settings by establishing an appropriate size of cohort and number of observations that would reduce observational bias. RWE could be initially used for supplemental applications of approved medicine in order to reduce safety considerations. Later, this approach could also complement randomized controlled trials (RCTs).

**Target precision medicine:** Individualized treatments are likely to become feasible at a large scale in the near-future. Identifying groups that might benefit from a drug before clinical testing could make clinical trials smaller and shorter, leading to improved efficiency and reduce exposure of subjects who are unlikely to benefit from a specific intervention.

**Aim for decentralized clinical trials:** Bringing clinical trials in patient communities can reduce infrastructure costs and increase the participation of patients or providers who could not be reached otherwise.

**Work with health care providers:** Working with providers and information technologists can allow sponsors of clinical research to serve as catalysts for creating a learning healthcare system where health delivery is integrated with knowledge generation. For example, this could be achieved by integrating clinical trials with information technology systems such as electronic health records (EMRs).

### TRENDS IN EARLY DRUG DEVELOPMENT

**RCTs Are Changing: Adaptive Designs Based on Basket, Umbrella, and Platform Trials**

RCTs are the gold standard for evaluating the efficacy and safety of drug products and are designed to evaluate pre-established statistical hypotheses. An important innovation in RCTs that can save costs from the earliest phase of clinical trial are adaptive designs, which allows for prospective plan changes in the elements of the clinical trial in order to make changes while the study is ongoing; for example, the dose levels of a drug can be altered if the product is less effective than expected. Adaptive designs can be used to address several hypotheses within a shorter period of time and, as such, increase the accuracy of a study while also speeding the development of the product. Adaptive designs are compatible with basket, umbrella, and platform studies.

**Basket trials** evaluate one targeted therapy on multiple diseases or multiple disease subtypes. Basket trials are typically conducted as single-arm phase II trials to evaluate proof-of-concept (POC). With basket trials, drug products would successively and independently be submitted to regulators.

**Umbrella trials** assess the effectiveness of several targeted therapies for one disease or group of diseases. Umbrella trials are often single-arm or randomized confirmatory sub-studies. With umbrella trials, patients don’t have to be re-screen several times for biomarkers to enroll in 4 separate trials.

**Platform trials** assess the effectiveness of multiple targeted therapies for a specific condition perpetually and the results of individual assessments are used to exclude or add targeted therapies or patient populations. Platform trials can be cost-effective, as multiple drugs can be analyzed at the same time in the same target populations⁵ by randomizing patients to different treatment arms.
In the near future, AI could be used to ease the task of early drug discovery by taking an active part in the process of identifying and validating drug targets, designing new drugs, drug repurposing, aggregating and analyzing biomedicine information, and patient recruitment decision-making. AI could also be used to predict feasible synthetic routes for drug-like molecules, pharmacological properties, protein characteristics and efficacy, drug combination, and drug-target associations. The identification of new targets and pathways with omics analysis becomes possible with the generation of new targets and biomarkers, personalized medicine based on omics markers and a better understanding of the relationship between drugs and disease.

At the present time, there are no developed drugs that have utilised AI approaches. In Europe, there are several companies promising to improve discovery via machine learning. The list includes Exscientia, which offers a drug design software that could be used in early clinical trials to discover small molecules and compounds that target single and bispecific targets. Another company, Healx, provides software that is supposed to help pharmaceutical companies match rare disease patients with drug treatment. This technology could be used to predict compounds that are likely to work well together. Finally, Owkin uses a dataset called Socrates that is meant to assist companies to create predictive models and optimize drug development using machine learning and deep learning.

**IMPROVING REGULATORY CONFIDENCE IN NOVEL EARLY PHASE CLINICAL DEVELOPMENT**

Many stakeholders active in the drug development industry believe regulators are often slow in adapting to the new realities of drug development. Whether this is the case or not, there are several strategies that can be used to improve their confidence in novel early phase development.

**Address the knowledge gap between innovators and regulators:** Innovators tend to understand their products better than regulators. A knowledge gap between those developing the products and those regulating it may lead to unnecessary delays. In the United States, the FDA Center for Devices and Radiological Health (CDRH) is
establishing mechanisms that would increase reviewers’ training via programs such as the Experiential Learning Program. The implementation of similar programs in Europe, as well as other parts of the world, would likely benefit both innovators and patients.

**Lobby for updated regulatory policies:** The regulatory frameworks based on which novel drugs are evaluated may need to change in order to adapt to clinical trials paradigms. For instance, combining a drug with a device can be constrained by a regulatory system that lacks elements which allow a proper evaluation of combination products. Collaborating with regulators in real time is necessary in order to ensure regulatory frameworks remain adequate.

**Improve predictive toxicology and efficacy:** Most drugs that have shown positive preclinical results don’t get approved due to unexpected adverse effects and lack of efficacy. Approaches that would provide drug developers with real-time human-based information with which to develop new therapies should also provide regulators a better scientific basis on which to make decisions. For example, pathway-based systems biology and organ-on-a-chip could deliver more efficient and accurate predictions of safety and efficacy.

**Take advantage of virtual tools:** Virtual tools may improve compliance with regulation. For instance, cloud-based analytical tools can be used to analyse documentation and detect missed or non-compliant elements.

**Promote regulatory convergence:** The International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)\(^6\) has contributed to the development of common regulatory standards across the globe. ICH was initially active in Europe, Japan, and the United States although it is increasingly participating in collaborations with regulators and industries from other parts of the world.

**Increase patient access to investigational drugs:** Laws should allow seriously ill patients the right to request an investigational drug treatment. The development of an infrastructure that would allow patients and providers to have knowledge of such treatments and easily access them would increase an innovator’s chance of proving the effectiveness of a new drug.

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**Regulatory Challenges in Europe: The Curious Case of Brexit**

Most companies located in the UK or that do business in the country are likely concerned about the effect Brexit will have on their business. A survey from the Royal Society of Chemistry\(^7\) shows that 72% of 5,800 chemistry professionals surveyed believe that a no-deal Brexit would have major negative effects on R&D.\(^8\)

Brexit is likely to impact the live science sector as a whole, as Marketing Authorisation Holders (MOHs) for Centralised Procedures have to be established in the EU or MOHs may need to transfer their marketing authorisation. More so, the Qualified Person Responsible for Pharmacovigilance (QPPV) has to be established in the European Economic Area (EEA) and Brexit will force it to relocate from London to a city in the EU. The European Medicines Agency (EMA)\(^9\) may face disruption as it leaves the UK and its relocation may also lead to several companies moving their headquarters along with it. Because EMA only employs EU citizens, the organization will lose expertise as it exists from the UK. A shortage of expert resources could reduce the speed of product approvals.

Finally, no one knows yet how the UK will regulate clinical trials after it leaves the EU, which may make companies interested in conducting clinical trials in the UK reluctant to do so for the time being.\(^10\)

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**CONCLUSION**

R&D in the pharmaceutical and biotechnology sectors is slowly but surely changing. Much of these changes are focused on saving the time and costs associated with traditional clinical trials while improving the efficiency of drug discovery. Widespread use of innovative protocol designs and technologies such as wearable devices and AI could bring new scientific and financial opportunities for the industry and, consequently, for the healthcare system. In Europe, drug developers and their collaborators could consider lobbying for regulatory policies that are adapted to the contemporary realities of drug discovery, as there is currently no clear mechanism that promises such flexibility. Another challenge to be considered from a regulatory point of view is Brexit, as its effects on early clinical trials conducted in the EU and the UK are yet to be determined.
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