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Opportunities for innovation in the design and execution of clinical trials

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"It is imperative that everyone with a stake in the viability of drug development, and the delivery of novel medicines to patients with unmet needs, come together collaboratively to work out practical solutions that will move us into a new era of productivity."

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We are all quite familiar with the challenges facing the pharmaceutical industry today that have contributed to declining productivity. The industry has matured to a point where the old pharmaceutical business model is unlikely to be sustainable. The cost of bringing a new medical entity to market has been estimated to exceed US$1.3 billion when capitalized costs are factored in [1]. Contributing to this unsustainable trajectory are the soaring costs and excessively high failure rates that continue to plague late-phase clinical development [2,101]. Innovative approaches to the design and execution of clinical trials hold promise for improving efficiency and reducing attrition rates, thereby addressing a significant factor underlying stagnation in the industry.

Indeed, opportunities for innovation in trial design and execution abound, and run the spectrum from technical and methodological aspects to operational and structural considerations. These opportunities include the application of novel tools and methodologies, flexible and adaptive designs, new infrastructures to support a 'learning health system' [3], open-sourced models, social media and web-based approaches.

Flexible trial designs

Much has been written and debated on flexible and adaptive trial designs [4], yet wide-scale adoption and integration into drug development strategies has lagged. The US FDA, in its draft adaptive design guidance for industry, has stated that the flexibility offered by adaptive design trials may be particularly useful in the exploratory phase of development by allowing for the initial evaluation of a broad range of choices for drug use, for discontinuation of suboptimal options, and for optimization by further adaptations within a sequential study [5]. In this guidance the FDA encourages sponsors to gain experience with these 'less well-understood' methods in the exploratory study setting, in part because there is less impact on regulatory approval decisions. The ability to adapt to rapidly changing information can be used to enhance flexibility in designs spanning, for example, from single ascending dose to multiple ascending dose studies, to seamless integration of proof-of-concept with dose ranging, and to target population enrichment strategies. A flexible trial design can also allow for adaptation within a single dose-finding trial to best assess the steepest part of the dose–response curve and to identify the minimal effective dose. While such approaches can improve efficiency, reduce timelines and make better use of available resources, significantly more up-front planning is required when compared with more traditional designs. In the end, this may well be worth the effort if successful identification of effective dose range and target patient population are achieved before heading into more costly late development programs.

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When it comes to late-phase clinical trials, there has been general reluctance from industry to use flexible/adaptive designs, other than blinded sample size re-estimation, with a few rare exceptions. Blinded sample size re-estimation is routinely applied by many industry sponsors as it provides a mechanism for appropriately adjusting the necessary sample size based on an interim analysis [6], and thereby increasing confidence that an appropriate sample size has been chosen to answer the primary study questions. For more substantial trial adaptations, one of the reasons for the low adoption rate has been the hesitancy of major health authorities to embrace such designs for pivotal trials that would serve as the basis of registration. Careful attention to details that safeguard the integrity of the trial and that establish processes for selection decisions must be agreed to in advance with regulators. This can require a lot of planning and can potentially delay the initiation of the trial, obviating much of the benefit. And flexible designs are not appropriate for every situation; rather, they should be considered in carefully selected circumstances with valid approaches to implementation. Areas for further exploration include the use of early interim analyses with biomarker-defined end points to better determine the timing of a final interim analysis based on the primary end point, and enrichment designs with interim decisions on whether to base the claim on the total study population or a subgroup [7]. More experience with such innovative designs in late-phase clinical trials in collaboration with health authorities should provide successful examples that will illustrate the value of adaptation and hopefully reduce some of the barriers to greater adoption.

Novel statistical tools & methodologies

Modeling and simulation can greatly aid in the successful design of clinical trials. Indeed, modeling and simulation tools are increasingly being used to support development strategies and health authority interactions throughout all phases of development [8,9]. Biological and pharmacological modeling can be very useful in the selection of a dose and dosing regimen that optimizes the target clinical benefit while minimizing undesirable adverse effects [10]. Data derived from such modeling exercises can therefore provide more objective justification for taking a specific dosing regimen into a Phase III trial, which may also be useful in addressing regulatory queries at the time of filing. Furthermore, the design of Phase III studies can be supported by prospectively simulating the outcomes of different trial designs, potentially improving success rates for compounds with efficacy that is intrinsically advantageous. Model-based drug development will be a cornerstone of the new development paradigm once there is greater experience and acceptance of its utility in supporting decision making across development. Additional applications include target and pathway evaluation in support of drug and disease models, portfolio analysis and product strategy, Go/No Go decision analysis, risk–benefit analysis and cost–effectiveness evaluations.

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Bayesian methodologies combine prior data with newly observed data, which may enhance the power of the updated information [11]. Using Bayesian approaches, limited available information may be maximized, power calculations for sample size may be enhanced, and potentially fewer studies and patients may be necessary to address the program's objectives. Modeling and simulation techniques for the purposes outlined above are also greatly facilitated by incorporating Bayesian principles where applicable. The detection of safety and efficacy signals can be made more efficient by deploying longitudinal modeling approaches to make use of all available information. Furthermore, the utility of early phase studies can be enhanced by incorporating the information obtained in them directly into later phase trials [11,12]. Bayesian modeling techniques are particularly useful in implementing these approaches.

Transforming clinical operations and the research infrastructure

The Institute of Medicine (IOM) has published a report on 'The Learning Health System and its Innovation Collaboratives' [3] that describes a vision to apply the best evidence for the healthcare choices of every patient and provider, while promoting discovery and innovation in healthcare. One of the transformation targets identified in this report is clinical research. Untapped opportunities exist to draw more frontline healthcare providers into the clinical research enterprise and make knowledge generation a part of the job description for everyone delivering healthcare. This includes an expanding set of new providers (e.g., nurse practitioners and physician assistants) practicing in alternative care settings such as pharmacies and convenient care clinics. These alternative settings have the potential to reduce some of the infrastructure costs and inefficiencies associated with trials using more traditional clinical investigative sites, while potentially accessing patients at their local point of care. Appropriate incentive systems will be required to engage busy healthcare providers and to make it worth their while to devote

time and effort to clinical research, unless it becomes integral to the delivery of healthcare itself. If this could be accomplished, frontline providers could serve as ambassadors for clinical research to patients, which could go a long way to surmounting the reluctance of many patients to participate in trials.

Use of advanced technology & informatics for disruptive innovation

The clinical research enterprise in western countries is being challenged by high costs, huge inefficiencies and difficulty finding and recruiting patients. For example, it has been estimated that less than 5% of adults diagnosed with cancer each year will be treated through enrolment in a clinical trial [102], and that the vast majority of clinical trial costs are accounted for by clinical sites. Greater use of health information technology has the potential to significantly improve efficiency and lower costs. This could be accomplished in part by reducing screen failure rates through pre-identification of patients who meet the inclusion/exclusion criteria using electronic health records. Open innovation models utilizing crowd-sourcing methods [103] can leverage the full breadth of input from internal and external experts, optimizing the design of trials and taking transparency to the next level.

A transformative approach to reduce costs and provide better access for patients has been piloted by conducting trials directly with patients, also called 'direct-to-participant' trials [104]. This method uses a single center overseen by a physician principal investigator, but otherwise has no clinical sites and no clinical investigators. The center interacts with participants via the internet or by email, and therefore has the potential to reach patients in remote areas regardless of proximity to a traditional clinical site. Recruitment is accomplished by the internet, consent is obtained via an interactive web-based process, and drug supply is distributed from a central pharmacy. Data collection can also be accomplished electronically [105], facilitated by smart phones or other hand-held devices. These devices could greatly hasten the incorporation of patient-reported outcomes into clinical trials, delivering on a growing demand for such data from patients, physicians and payers that goes well beyond the registration needs of regulatory authorities. While support from regulatory bodies and ethics review boards has been achieved for over-the-counter and marketed products, the next frontier is to explore the utility of this approach to products in development and to end points other than patient-reported outcomes. This will require further discussions with health authorities, and may ultimately be achieved for selected disorders and some investigational therapies in the near future. However, if these novel methods could be applied more broadly, incredible efficiencies in trial costs and in patient enrolment could become a reality.

Opportunities for innovation: moving forward

The pharmaceutical industry is facing a productivity challenge. The business model should change if we are to reap the full benefit of having sequenced the human genome and deliver on the promise of a continued stream of breakthrough therapies. A key component of the new paradigm must include a transformed clinical research enterprise and the integration of novel approaches, some of which are outlined above. Opportunities for innovation spanning scientific, technical and operational domains have been identified, with many credible solutions already on the table. It is imperative that everyone with a stake in the viability of drug development, and the delivery of novel medicines to patients with unmet needs, come together collaboratively to work out practical solutions that will move us into a new era of productivity.

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