New Strategies to Modernize Clinical Trials to Advance Precision Medicine

We look forward to working with our many stakeholders to make the promise of precision medicine a reality for more people.

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Statement by FDA Commissioner Scott Gottlieb, MD, on new strategies to modernize clinical trials to advance precision medicine, patient protections and more efficient product development

Modernizing clinical trials is an agency-wide priority. As more diseases are being redefined based on genomic subtype, researchers have more novel targets and more opportunities to precisely modulate or even repair the basic biological drivers of illness. Precision guided medicines can demonstrate strong efficacy signals in early clinical trials, including in trials where small groups of patients are selected based on biomarkers or other criteria suggesting they're likely to benefit. These trials can potentially allow earlier regulatory assessment of benefit and risk. When the agency can make a positive approval decision, patients can gain earlier access to important new therapeutic options. To take advantage of these innovations, the agency is also seeking new ways to modernize its approaches to accommodate these novel opportunities.

The FDA isn't alone. The advent of precision medicine is challenging the entire medical research ecosystem to develop more efficient approaches to testing and developing diagnostics and therapeutics, to harness the full potential of science to reduce the suffering, death, and disability caused by complex human illnesses. The agency is committed to developing a regulatory framework for precision medicine that generates robust evidence of product safety and efficacy as efficiently as possible, including frameworks that are more carefully suited to the kinds of precision technologies that underpin new treatments.

But these opportunities can be delayed or stymied by a clinical research enterprise that is often extraordinarily complex and expensive. Efforts to streamline medical product development based on advancing science can be frustrated by legacy business models that discourage collaboration and data sharing, and the adoption of disruptive technologies that make clinical research more effective. Without a more agile clinical research enterprise capable of testing more therapies or combinations of therapies against an expanding array of targets more efficiently and at lower total cost, important therapeutic opportunities may be delayed or discarded because we can't afford to run trials needed to validate them.

The agency has worked closely with stakeholders, including the Clinical Trial Transformation Initiative, to identify innovative trial designs, evaluate the role of decentralized clinical trials and mobile technologies, and help validate novel endpoints that can enable trials to generate reliable evidence needed to assess product safety and efficacy more efficiently. For instance, the FDA has pioneered master protocol trial designs that can evaluate, in parallel, different drugs compared to their respective controls or to a single common control. These trials can be updated to incorporate new scientific information, like novel biomarkers, as medical science advances. The infrastructure for these trials can last for decades. This reduces administrative costs and time associated with standing up new trial sites for each drug candidate.

Unfortunately, we've seen a continued reluctance to adopt innovative approaches among sponsors and clinical research organizations. In some cases, the business model adopted by the clinical trial establishment just isn't compatible with the kind of positive but disruptive changes that certain innovations can enable. We appreciate that scientific and technical complexity is a real and ongoing challenge, but industry and academia also need to invest in and leverage these approaches and develop new incentives that reward collaboration and data sharing across the clinical research enterprise.

New research paradigms are needed to break down barriers between real world data and clinical research, so that evidence can be shared rapidly to improve both domains across a learning health care system. For instance, more trials can incorporate data from electronic health records, and adopt electronic informed consent, to enroll more patients in clinical trials closer to where they live and work. This can reduce barriers to clinical trial participation and accelerate researchers' ability to ask and answer important questions.

We're committed to advancing more of these approaches through additional guidance and workshops that we're announcing that are focused on overcoming bottlenecks to modernizing trial infrastructure.

This week, we released guidance for sponsors on how they can incorporate patients with more challenging health conditions into oncology clinical trials. This includes patients with brain metastases or previous malignancies; patients with organ dysfunctions, as well as adolescent and pediatric patients. Inclusion of these patients can make trials more representative of real world oncology care.

Today, we're releasing additional guidance for industry on strategies that can support the development of precision medicines, and guidance on risk-based monitoring that can be accomplished through the incorporation of more computerized systems for effective oversight. These guidances, Enrichment Strategies for Clinical Trials to Support Determinations of Effectiveness of Human Drugs and Biological Products, and A Risk Based Approach to Monitoring of Clinical Investigations: Questions and Answers Guidance for Industry, can help facilitate efficient development of novel innovations, while also generating the robust evidence needed to better assess product safety and efficacy.

We're also releasing a final guidance for industry, Severely Debilitating or Life Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals (SDLTHDs). This guidance is intended to streamline the development of pharmaceuticals used to treat patients with SDLTHDs, other than cancer, while protecting patients' safety and avoiding unnecessary use of animals in the conduct of trials.

The guidance addresses the appropriate use of non-clinical tests, both in vitro and in animal models. These approaches can facilitate streamlined development programs by improving sponsors' understanding of drug or biologic effects on biological pathways, or potential organ toxicity, while still protecting patients' safety and avoiding unnecessary use of animals. These methods are in accordance with the 3Rs (reduce, refine, replace) — principles that govern the proper conduct of non-clinical research and that the FDA supports. Non-clinical evaluations include pharmacology, safety pharmacology, general toxicology, genotoxicity, reproductive toxicology, carcinogenicity, immunotoxicity, photosafety testing and pharmacokinetics.

This guidance applies to drugs used both to treat the active disease and to prevent the recurrence of a life-threatening or debilitating event. Some examples of SDLTHDs are multicentric Castleman's disease, aplastic anemia, paroxysmal nocturnal hemoglobinuria, hemophilia and sickle cell disease.

Enriched Trials

Enrichment is also a key strategy in the development of precision medicine. Under these approaches, treatments are targeted at groups of patients based on clinical laboratory tests, genomic or proteomic factors. Enrichment strategies rely on the selection of patients for clinical trials based on one or more characteristics intended to demonstrate the safety and/or effectiveness of the drug or biologic in selected populations. Enrichment can make it easier to detect a drug's effect (if one is present) in a biomarker selected population — for instance, HER2 Neu+ positive breast cancer — than it would be in a larger population that hasn't been prespecified, and where only a select population of patients would respond.

These approaches can allow signal detection in smaller clinical trials, or trials of shorter duration, compared to ones that are open to "all comers." For instance, when the high-responder population constitutes only a small fraction of all patients, such as 20 percent (a common situation in oncology settings), enrichment may generate evidence of effectiveness in a small study, including only potential responders, when showing any effect in an unselected population where only 20 percent could respond would be much more difficult. The information gleaned from these approaches can also guide clinical practice, to help doctors get the right treatment to the right patient at the right time. The same information used to select patients based on their likelihood of responding positively to a drug in a trial can be used to guide real world care.

The guidance we're issuing today, Enrichment Strategies for Clinical Trials to Support Determinations of Effectiveness of Human Drugs and Biological Products, can help expand the use of these approaches and facilitate development of innovative enrichment strategies in tandem with advancing science.

Risk-Based Monitoring

Protecting human subjects in trials is another critical part of the FDA's mission. Sponsors of clinical investigations involving human drugs, biological products, medical devices, and combinations thereof are required to provide oversight to ensure adequate protection of the rights, welfare and safety of human subjects and the quality of the data submitted to the FDA. The regulations are not specific about how sponsors are to conduct such monitoring; a range of approaches to monitoring are compatible with the regulations.

Traditional on-site monitoring of each clinical site to evaluate study conduct and perform 100 percent source data verification is highly resource intensive and may account for up to a third of the total clinical trial cost. But traditional on-site monitoring that is overly focused on source data verification doesn't guarantee data quality.

Risk-based monitoring, as a component of a sponsor's overarching quality risk-management systems and trial-specific quality by design programs, can help to provide more efficient oversight of trials, while still protecting human subjects and assuring data integrity. To support greater use of efficient risk-based monitoring, today's guidance on A Risk-Based Approach to monitoring of Clinical Investigations: Questions and Answers provides guidance to industry on implementing risk-based monitoring of investigational studies of human drug and biological products, medical devices, or drug and device combinations.

This guidance can help sponsors tailor monitoring plans to the needs of the clinical investigation, while focusing on those risks that have the greatest potential to adversely affect study quality, including critical risks to the maintenance of the rights, safety, and welfare of trial participants, and the collection and analysis of key safety and efficacy endpoint data. Risk based monitoring can be advanced using computerized algorithms that enable remote and central trial monitoring, as well as the development of advanced analytics that can be used to monitor data integrity as a trial is in process.

We look forward to working with our many stakeholders to support the development of these modern approaches and make the promise of precision medicine a reality for more patients.

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