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January 19, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA-2023-N-4489; Enhancing Adoption of Innovative Clinical Trial Approaches; Public Workshop

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA/ the Agency) for the opportunity to submit comments regarding the request for information and comments on the **Enhancing Adoption of Innovative Clinical Trial Approaches; Public Workshop.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place. BIO appreciates the opportunity to provide comments to the Agency in advance of its public workshop, and looks forward to participating in the workshop.

1. *What are the key challenges or barriers, perceived or actual, that may hinder the implementation and adoption of innovative approaches in clinical trial design, conduct, and execution?*

Industry routinely invests in innovative tools and approaches to develop better medicines that meet the needs of patients, such as decentralized clinical trials (DCT), model-informed drug development (MIDD), drug development tools (DDT), complex innovative trial design (CID), patient-focused drug development (PFDD), and leveraging real-world data (RWD). Industry agrees with the FDA that pilot programs and guidances are important to aid implementation in clinical development programs. To this end, we commend the Agency for its many efforts to advance clinical trial innovation, including topic-specific pilot programs (e.g., for MIDD, RWD, and CID, DDT qualification programs), and dedicated initiatives to advance other areas of innovation (e.g., PFDD, DCTs, and digital health).

In general, there remains a degree of hesitation among drug developers regarding the adoption of innovative approaches for clinical trials which is largely attributed to a lack of clarity, consistency and dedicated Agency resources. While the FDA encourages industry to explore new methodologies, such as new study designs and approaches, industry still finds these methodologies risky to implement due to continued uncertainty regarding the regulatory outcome. For the industry to effectively design and conduct innovative clinical trials, the FDA's timely, substantive, and interactive scientific input is needed to help reduce regulatory uncertainty. Further, the industry would benefit from more fluid engagement, including interactive clarification opportunities through interactive Type D or "follow-up opportunities" with

the FDA. Below, we have outlined specific considerations across multiple innovative tools and approaches:

Decentralized Clinical Trials:

With respect to DCTs, the FDA has proposed various approaches (e.g., use of home health for remote use instead of onsite practices) to ease the burden on the patient and clinical site and facilitate broader patient enrollment[1] However, restrictions on the use of telemedicine or shipment of investigational medical products (IMPs) across state lines impede the widescale adoption of DCT. We would welcome the FDA working with stakeholders in the states to help remove these barriers to trial participation, similar to the Agency's actions during the COVID-19 pandemic, when the FDA's leadership greatly enabled the ability of sponsors to conduct DCTs by facilitating cross-state shipments of IMP. There would be more opportunities for scaling direct-to-patient IMP delivery if the Agency were able to help mitigate some of these state-level barriers.

In addition, current state telehealth legislation presents an obstacle to remote trials. With respect to physician licensing, this obstacle results in one of the following outcomes:

1) the sponsor needs a site with an investigator licensed in every state from which they wish to recruit participants,
2) the sponsor needs to retain a site with investigators who are licensed in multiple states (and even this presents coordination challenges to ensure the licensed investigator is conducting visits for participants in relevant states),
3) the sponsor must limit recruitment to states where licensed investigators are available from the selected sites.

Lastly, DCTs can be more challenging because of limited adjustments to traditional regulatory frameworks. For example, if FDA requires 1572s for sites performing limited routine care tasks and testing (or requires a central investigator to oversee activities at sites outside of his or her control), DCT designs are discouraged without a corresponding benefit to public health. Likewise, the lack of clarity around issues like data security and integrity in FDA guidance hinders DCT adoption. Accordingly, we recommend the Agency consider providing further clarity on PI-oversight/1572s in DCTs such as decision trees or flow charts to help delineate oversight responsibilities.

Model-Informed Drug Development and Synthetic Controls:

The MIDD Paired Meeting Program launched in PDUFA VI is intended to facilitate the development and application of novel modeling approaches in the context of specific drug development programs. This program has generated substantial industry enthusiasm and engagement and, while the general perception of this program has been positive, experiences have been inconsistent, with clinical reviewers sometimes at odds with their counterparts from the FDA's Office of Clinical Pharmacology.
Moreover, the MIDD program has not resulted in systematic changes to reviewer practices or views. For example, although the program emphasizes the potential for modeling to "optimize drug dosing/therapeutic individualization in the absence of dedicated trials" and the application of MIDD to dose optimization is an explicit goal, clinical reviewers from FDA's Oncology Center of Excellence (OCE) recently stated at a

[1] FDA Draft Guidance – Decentralized Clinical Trials for Drugs, Biological Products, and Devices, May 2023 - https://www.fda.gov/media/167696/download

public workshop that MIDD approaches can only provide complementary evidence to randomized dose comparison and any decisions will continue to be based on clinical trial data.

This raises serious concerns about the future of investing in MIDD approaches. The complex nature of clinical trials inevitably means that one or two doses are used in a given protocol. Further, insisting on clinical trials to determine dosing is unrealistic, given that the limited number of patients belonging to specific subpopulations, especially in clinical trials developing products in limited populations (e.g., rare disease, pediatrics) may not be statistically robust enough to allow for scientifically sound conclusions. Modeling, therefore, offers an attractive, evidence-based alternative to determine appropriate doses for specific subpopulations.

Furthermore, patient-focused trials could be facilitated by addressing trials participants' desire to be on active treatment through broader use and acceptance of synthetic controls. Without continued support from the Agency, there is a risk of sponsors abandoning modeling approaches with the ultimate price being paid by patients.

Drug Development Tool Qualification:

Novel DDTs such as biomarkers and clinical outcome assessments (COAs) play an important role in advancing clinical trial innovation. FDA established the DDT qualification process to assess the utility of biomarkers and COAs independently from drug development programs, allowing stakeholders from academia, patient groups, public-private partnerships, and others to participate in and contribute to drug development. Although the program was first initiated following a series of reports from the Critical Path Institute from 2004 and 2006[2] and formalized in statute in 2016 as part of 21st Century Cures, few DDTs have been qualified, including only 7 COAs[3] and 8 biomarkers[4], with the most recent qualification taking place in 2020. Engaging in the DDT program is a long and arduous process that can typically take at least 5 - 10 years. Over this long period, the Agency's views can shift considerably. Ultimately, there is only an incentive to continue participating in this effort if the FDA will qualify COAs or biomarkers via the DDT program in drug development in a reasonable timeframe.

Complex Innovative Trial Design Paired Meeting Program:

Sponsors have experienced gaps between pilot programs for innovative approaches and the FDA's regular review process outside these programs. There are successful examples of implementing innovative study designs in the CID Paired Meeting Program. It's also well acknowledged by program participants that the partnership, significant contributions, and feedback provided by the FDA through the pilot process are key factors driving its success. To advance the use of innovative approaches in studies outside the CID Paired Meeting Program, adequate review and consideration of the

[2] Woodcock, J., and Woosley, R. "The FDA Critical Path Initiative and Its Influence on New Drug Development." Annu. Rev. Med. 2008. 59:1–12. – https://www.c-path.org/pdf/FDAcriticalpathinitiativeinfluenceonnewdrugdevelopmentWoodcockWoosley.pdf.

[3] FDA CDER Qualified Clinical Outcome Assessments – https://www.fda.gov/drugs/clinical-outcome-assessment-coa-qualification-program/qualified-clinical-outcome-assessments-coa.

[4] FDA CDER List of Qualified Biomarkers – https://www.fda.gov/drugs/biomarker-qualification-program/list-qualified-biomarkers.

innovative design proposals and feedback by FDA, specific to the proposed approach in the context of study of interests, is essential. However, the feedback often received from reviewers is limited to general and common potential risks of innovative design compared to conventional approaches. Because of the nature of innovative/complex design, it usually requires sponsors to spend significant time and effort on methodological research and computationally intensive simulation studies for a comprehensive evaluation of operating characteristics. It would be beneficial to sponsors if FDA could ensure that FDA experts conduct a thorough review to appropriately evaluate the study design, analysis plan and simulation report and provide comments specific to the proposal, to better understand in which conditions these approaches can be proposed and accepted by FDA.

Additional Innovative Approaches:

Other innovative areas where there is a need to address challenges with regulatory clarity and acceptance include PFDD, real world evidence (RWE), and acceptance of digital health endpoints. With regard to PFDD, the lack of clarity on how and when the FDA uses patient input to inform regulatory decision-making presents challenges for implementing innovative approaches to patient engagement. The time and effort expended by patients to support the generation of patient experience data (PED) are significant and it is important that patients have reason to believe that their participation in drug development has a meaningful impact to the process. Greater transparency regarding the use of PED in the context of medical product reviews is critical to supporting the future of PFDD. Similarly, the FDA appears reticent to accept digital endpoints, at times imposing high burdens for tool validation, even for simple tools. For RWE, BIO suggests FDA leadership finds ways to work with review divisions to be more accepting of RWE to support effectiveness, especially for hybrid models where it supplements more traditional data collection while maintaining the benefits of randomization.

Policy uncertainty underlies many of these issues, exacerbated by the different perspectives regarding the oversight of innovative approaches by the different FDA medical product centers (CDER, CBER, CDRH, OCE), and the lack of integration of programs that were initiated as pilots into normal review practice. In addition, the lack of global harmonization with other regulatory bodies deters sponsors from considering innovative approaches, especially pertaining to multinational trials.

Non-FDA Related Challenges:

External to the FDA, Institutional Review Boards (IRBs), both local and central, can hinder the adoption of innovative approaches due to their tendency to be conservative when reviewing study designs, given the lack of trust, comfort or experience in the use of innovative approaches. For example, if a sponsor wants to implement a new approach that can reduce the burden on the patient, in the absence of clear guidance, an IRB may delay approval. IRBs are also sometimes slower to embrace new technologies due to privacy concerns.

Furthermore, the different approaches and resources across sites and investigators can present challenges. For example, sites' approaches to acquiring participants' written informed consent may vary, including different preferences on language, site mapping, and the potential use of Personal Identifiable Information, making it difficult for sponsors to propose innovative

processes. Informed consent forms do not always reflect patients' benefit-risk calculus and preferences: while different approaches may be expected when there are specific concerns within a clinical specialty, many of these differences occur without a clear connection to clinical context. Sponsors wishing to use electronic consent forms to ease the burden on sites and patients often find that clinical sites do not have the necessary infrastructure to adopt electronic consent forms. In addition, the lack of global alignment on the use of electronic means to collect consent discourages their use in global trial settings.

Lastly, there are financial barriers. Clinical sites are often impacted by resource constraints to complete a sponsor's study, and this is especially challenging for innovative studies incorporating more complex protocols and procedures. Financial burdens can impact both the clinical site and sponsor as novel, more complex approaches may incur more costs.

2. *Provide examples of instances where integrating new innovations into existing programs or systems became particularly challenging. Are there specific actions that CDER or others could take to enhance implementation and adoption of innovative approaches in clinical trial design, conduct, and execution?*

It would be beneficial for FDA to spotlight innovative practices successfully adopted by companies and how other companies might apply similar approaches. Also, initiatives such as the CID Paired Meeting Program, already undertaken by the FDA, hold significant potential for promoting the adoption of innovative approaches. Sharing of public case studies[5] has played a key role in enhancing the industry's understanding of the regulatory perspectives of the Agency and potential concerns that need to be addressed.

We further recommend a collective effort towards the adoption of innovative technologies, such as direct transfer of site electronic medical record data to sponsor electronic data capture systems, to support reduction in site burden and ensure data are readily available in real time for sponsors. Site uptake in using this type of technology has been slow for various reasons, including site policy, sites having their own proprietary technology for this activity, and upfront work to implement. However, if this were more broadly implemented, it could reduce cycle times of trials.

Information sharing including webinars and publications on the CID Paired Meeting Program trial design case studies has been extremely useful for the sponsors to learn from real examples and maximize the impact of such program. One approach the Agency could adopt to enhance information sharing for other innovative clinical trial approaches is to expand upon the approach taken with the CID paired meeting program where the Agency organizes public webinars to discuss anonymized case studies with novel methodologies and/or designs from sponsors. The discussion would focus on whether these designs were accepted by the Agency or rejected, with rationales. We also recommend that FDA includes in public discussion how they plan to integrate learnings from pilot program into normal review practices.

Further, FDA could consider ways to make its decisions (potentially including the full review details, for select health authorities) more transparent. The FDA already does this primarily through Project Orbis and we encourage the expansion of this practice.

[5] FDA Complex Innovative Trial Design Meeting Program - https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

3. *Do certain therapeutic areas or types of trials face unique barriers or challenges to implementing innovative approaches? If yes, please explain.*

While innovative approaches can offer the most significant advantages in pivotal trials, the lack of regulatory clarity or necessary infrastructure leads to hesitancy among sponsors to adopt innovative practices. The impact of this is particularly significant during Phase 3, with larger populations that may be more dispersed. For instance, DCT approaches may not be feasible in some countries due to a lack of the necessary healthcare infrastructure or divergent regulatory requirements.
Examples of successful implementation of innovative clinical trial approaches are more often seen in rare diseases compared with non-rare disease therapeutic areas, and the bar for accepting innovative designs is considerably higher for non-rare diseases, even if it is also severe or life-threatening or there are challenges that make conventional design infeasible. However, we also note that in the case of slowly progressing rare diseases where the use of placebos may be infeasible and unethical, greater flexibility regarding the use of external controls is needed, particularly in light of recent FDA guidance[6][7] that set a very high bar for their use. We recognize the acceptability of innovative approaches can vary across indications and therapeutic areas because of the level of unmet needs and unique considerations resulting in a different benefit/risk calculation, but it would be helpful if the Agency provided general standards or principles on the balance between trial efficiency/patient centricity and the risk of bias/type I error, especially different considerations among different indications and therapeutic areas.

Moreover, in oncology, stricter regulations in relation to Project Optimus, with requests to implement randomization comparison in Phase 1, before sponsors know if a molecule has strong signal of activity and what indications are sensitive to the investigational therapy, can be challenging. This could discourage drug developers (especially small companies) from running Phase 1 studies in US and increase the burden/complexity for sites and in some cases for patients (i.e., more patients to be tested in situations where retrospective use of data may help to trim down the number of patients needed for decision-making, or where lack of sufficient activity may induce to stop the program).

4. *What challenges emerge when trying to apply innovative approaches in new areas (e.g., in a new therapeutic area or different trial types)? What are the considerations that become more important as innovation is scaled and approaches wide-spread implementation? How can stakeholders in the clinical research enterprise address these considerations effectively*

Industry experience from a clinical systems perspective suggests that innovative approaches in new areas typically result in system constraints or deviations from the systems' core functionality, requiring companies to implement heavily customized programming. Greater consistency would result from aligning elements of different innovative trial design approaches agreed within the industry as best practice and then aligning the clinical systems to match. This

[6] FDA Draft Guidance – Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, February 2023 – https://www.fda.gov/media/164960/download.
[7] FDA Final Guidance – Rare Diseases: Considerations for the Development of Drugs and Biological Products, December 2023 – https://www.fda.gov/media/119757/download.

would involve the inclusion of both sponsors and third-party suppliers in defining these best practices.

Electronic Clinical Outcome Assessments (eCOAs), electronic medical records (EMR), and electronic data capture (EDC) are examples of technological advances that have become state of the art in recent years; they demonstrate that significant innovation in the conduct of clinical trials is possible. For example, eCOAs are widely used in DCTs, showing there is an appetite for well-established technologies with experienced vendors. However, with respect to DCTs, some clinical trial sites fear that technological advances may limit their role in the conduct of trials. Engagement with sites is critical to increase their comfort with the use of DCT technological advances and to realize the full potential of innovations in clinical trial design.

5. *What are effective ways to enhance and coordinate communications with CDER (e.g., review divisions, compliance/inspectorate) or across other FDA stakeholders as new clinical trial innovations are implemented? Please describe the specific stakeholders, areas, or aspects that may benefit from enhanced communication or coordination.*

Guidance on digital health technologies (DHTs) is generally helpful, and we particularly appreciate FDA's recent publication of the final guidance *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*. Sponsors and vendors are pushing the boundaries of what is possible here and trying to adopt more innovative clinical trial procedures. However, an emerging challenge is the proliferation of options without any standardization of data, front end useability, or easy data integrations between the various tools. We believe FDA has an opportunity to accelerate adoption of DHTs by voicing support/advocating for industry efforts regarding harmonization and standardization and reviewing/contributing to any outputs generated.

As we are trying to initiate innovative clinical trials, it is important to reach global alignment on protocols to allow for global protocols. FDA's role as a leader in innovative clinical trials puts them in a good position to be working globally with health authorities so that there is understanding across the globe about what innovative clinical trial approaches are acceptable. Especially for rare diseases where enrolling each patient is very important, global studies that are registered across multiple regions allow for products to be efficiently developed to allow patient access to safe and effective treatments.

Sincerely,

/s/
Derek Scholes
Sr. Director, Science & Regulatory Affairs
Biotechnology Innovation Organization