Biotechnology Innovation Organization
1201 New York Avenue, NW
Suite 1300
Washington, DC, 20005
(202) 962-9200

August 24th, 2026

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. FDA-2023-D-5259; Master Protocols for Drug and Biological Product Development

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the Agency's Draft Guidance, *Master Protocols for Drug and Biological Product Development.*

BIO is the premier biotechnology advocacy organization representing biotech companies, industry leaders, and state biotech associations in the United States and more than 35 countries around the globe. BIO members range from biotech start-ups to some of the world's largest biopharmaceutical companies – all united by the same goal: to develop medical and scientific breakthroughs that prevent and fight disease, restore health, and improve patients' lives. BIO also organizes the BIO International Convention and a series of annual conferences that drive partnerships, investment, and progress within the sector. Learn more at bio.org.

Sincerely,

/s/
Neil Ichiro Laruan
Director, Science & Regulatory
Biotechnology Innovation Organization

General Comment(s):

BIO thanks FDA for issuing this revised draft guidance on master protocols and supports the Agency's continued efforts to modernize the design and conduct of basket, umbrella, and platform trials. BIO appreciates that master protocols can reduce duplicative infrastructure, streamline data collection, and accelerate evidence generation across multiple investigational products and disease populations. BIO offers the recommendations below to help ensure the final guidance reflects the operational realities of running these trials while preserving the flexibility necessary to support master protocol applications across a diverse range of therapeutic areas.

BIO recommends FDA provide recommended terminology or sample protocol text for complex design elements addressed throughout the guidance. This could cover control-related elements, such as shared control arms, concurrently eligible controls, nonconcurrent controls, drug-specific eligibility criteria, changing randomization ratios, and re-enrollment after washout, as well as blinding-related elements, such as multiple-dummy designs, partial blinding, matched controls, and open-label justification. Recommended language for these elements would help ensure protocol text remains precise and aligned with the statistical analysis plan (SAP). FDA should also clarify which elements are expected to be described in the protocol versus the SAP or a statistical simulation report, particularly for success criteria, interim analyses, borrowing assumptions, treatment effect estimation, and the handling of concurrent or nonconcurrent controls.

BIO also recommends the guidance clarify how its concurrent-control principles relate to FDA's guidance on externally controlled trials, given that both address related methodological issues, including borrowing, temporal drift, and exchangeability, even though this guidance excludes external controls from scope. Clearer terminology would also help, including distinctions between concurrent and contemporary controls, time-adjusted and cohort-adjusted analyses, and alignment with terminology in the statistical literature. Finally, guidance on implementing weighting approaches, such as inverse-probability weighting, and reporting effective sample size and other borrowing diagnostics would improve transparency and consistency across submissions.

Regarding adaptive platform trial conduct, the guidance would benefit from more clearly recognizing the operational role of adaptive design elements, including common calendar-time interim analyses, to support efficient resource allocation while preserving blinding and trial integrity. The guidance should also provide additional clarity on expectations for randomization in platform trials, such as the selection and justification of randomization ratios when multiple investigational products share a common control arm. Sponsors would benefit from guidance on when unequal allocation, shared-control allocation, or response-adaptive randomization may be appropriate; how to update randomization probabilities when arms are added, stopped, or otherwise modified; and how to reflect these strategies in simulations used to evaluate operating characteristics. This should also clarify when substudy-level randomization may be omitted in platform trials with sequential, non-overlapping substudies, such as when only one substudy is enrolling at a given time or assignment is otherwise driven by eligibility or site availability.

BIO seeks clearer expectations for evaluating operating characteristics, power, precision, control-arm comparability, and Type I error control, an area where regulatory messaging has not always been consistent. BIO further recommends that FDA provide a clearer taxonomy of multiplicity considerations in master protocols, distinguishing among multiplicity arising from multiple investigational products, substudies, populations or disease cohorts, endpoints, interim analyses, and adaptive decision rules. These clarifications would help sponsors determine when family-wise error rate control, false-discovery-rate approaches, hierarchical testing, gatekeeping strategies, or other approaches may be appropriate, and when adjustment may not be necessary based on the inferential objective.

Expectations for head-to-head comparisons between investigational arms within a master protocol should also be clarified. In some platform trials, the availability of contemporaneously randomized investigational arms may support direct comparisons to inform clinical development, regulatory decision-making, or potential labeling. Sponsors would benefit from guidance on when such comparisons may be considered exploratory versus confirmatory; how superiority or noninferiority hypotheses between investigational arms should be pre-specified and justified; and how differential timing of arm entry, control-arm sharing, follow-up duration, and potential changes in standard of care should be addressed.

Guidance on borrowing across substudy populations in basket trials should also be expanded, including examples illustrating how one substudy may provide substantial evidence of effectiveness while related substudies contribute confirmatory evidence, and what level of confirmatory evidence would be expected. Clarifying the circumstances under which evidence generated under a master protocol may be considered adequate to support a marketing application, whether independently or together with complementary evidence, would also help sponsors align development and evidentiary strategies early in development.

The guidance would also benefit from additional details on safety monitoring and data-sharing expectations in master protocols, particularly where multiple investigational products, sponsors, or substudies are evaluated under a shared infrastructure. Sponsors would benefit from clarification on expectations for unified safety monitoring plans, cross-arm safety signal detection, data access and firewalls, sponsor responsibilities for reviewing and acting on emerging safety information, and the potential impact of emerging safety issues in one substudy on ongoing or planned substudies. Clearer guidance would help support timely safety oversight while preserving blinding, trial integrity, and appropriate separation of confidential information across investigational products. Relatedly, BIO recommends FDA clarify how partial clinical holds apply to individual substudies under different IND structures, such as whether expectations differ between a single master protocol IND and separate substudy INDs, and how a hold on one substudy is expected to affect shared infrastructure, ongoing recruitment, and participant management across the remainder of the platform.

FDA should extend the consent-simplification approaches described in its existing informed consent guidance to platform trials, where a single upfront consent form may become lengthy as new treatment arms are added over time. BIO also suggests that FDA include substudy-specific nomenclature in an appendix to support consistent regulatory administration across sponsors. Because the guidance addresses updates to an already-existing master protocol but not the scenario in which a standard stand-alone trial is amended after study start to incorporate a master protocol design, BIO recommends that FDA also provide guidance on how sponsors should approach that transition. Given the adaptive nature of many master protocols, examples of the types of modifications during trial conduct that would generally warrant additional FDA engagement would also help sponsors maintain regulatory alignment as trial evolves.

BIO shares FDA's commitment to ensuring the United States remains the global standard for pharmaceutical innovation and regulatory rigor and appreciates efforts such as this guidance under Operation TrialBlazer to advance that shared goal. Because umbrella, basket, and platform trials are frequently conducted as multi-regional trials intended to support submissions across jurisdictions, BIO also recommends the guidance encourage early engagement with other health authorities where appropriate, particularly where protocol adaptations, control-arm strategies, or statistical methodologies may affect the global acceptability of the resulting evidence, and reference relevant international initiatives such as ICH E20 to promote consistency in terminology and trial planning across regions. BIO thanks FDA for its continued engagement with stakeholders as master protocol design and analysis approaches continue to evolve. Additional line-item comments and proposed edits are provided in the table below, intended to provide additional clarity, ensure regulatory expectations remain fit for purpose, and facilitate consistent implementation across sponsors.

Line Items:

Section number (i.e. 1.0 , 1.1, or 1.2.3)	Lines	Comment and rationale	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
III. A	135 - 136	This sentence seems superfluous and may set a strong perception that for with a master protocol trial, multiple trials are a must. • Would there be an expectation for a replicate ph3 trial that is not a master protocol? • Would it be a problem if both ph2 and ph3 would be from a master protocol. • If only concurrent control data are allowed to be used (following sections), it would seem restrictive. • Platform trials in rare indications may not allow for “replicate” trials.	Recommend FDA remove the statement, "A development program that includes a master protocol will often also include stand alone trials, given the different types of data needed to support drug development." This information is understood from common drug development regulations and practice and may set here wrong perceptions, such as “because of the master protocol additional studies will be needed”.
III. A	176	The guidance states “Possible approaches include stratifying by the time period or inverse weighting by probabilities of treatment assignments.” It is not clear how weighting by probability of treatment assignment would be implemented in practice, given the non-concurrent nature of enrollment.	Request clarification of the suggested weighting by probability approach, possibly adding an example. If the effect of timing is included the probability of assignments should result as “0” for the non-concurrent time periods. Conventional weighting on baseline covariates should be done ignoring the "calendar time".
III. B	207 - 318	The guidance discusses concurrent controls and nonconcurrent controls and refers to other guidance on the use of external controls. The general recommendation in the master protocol guidance on disregarding non-concurrent control data is overly restrictive and may as such conflict with guidance on the use of external controls or Bayesian methods.	Request FDA consider including a brief statement acknowledging that future use of hybrid designs incorporating external or real-world-data controls may raise similar methodological considerations regarding exchangeability, temporal drift, and borrowing.
III. B	207 - 318	The guidance could be clearer in regards to what constitutes a non-concurrent control and when it is (more) permissible to use non-concurrent controls. Marschner and Schou (DOI:10.1002/bimj.202300334) outline a framework that makes clear the difference between concurrent and contemporary, and the difference between time-adjusted and cohort-adjusted analyses. Some of the terminology could be fruitfully adopted.	Recommend FDA adopt some terminology from the Marschner and Schou (DOI:10.1002/bimj.202300334) framework to differentiate between concurrent and contemporary, and the difference between time-adjusted and cohort-adjusted analyses.

III. B	245 - 247	The guidance states, “Nonconcurrently randomized participants and concurrently randomized participants who could not have been randomized to the drug should not be included.” It contains two situations: “nonconcurrently randomized participants” and “concurrently randomized participants who could not have been randomized to the drug”. The statement states that in both cases the participants should not be included. The second case is clear while for the first one it is unclear, whether this is a general recommendation to not include non-concurrently randomized subjects, or just those, who could not have been randomized to the drug (due to subprotocol in/exclusion criteria).	Suggest the Agency rephrase the sentence to “Concurrently randomized participants who could not have been randomized to the drug and nonconcurrently randomized participants should not be included.” or “Nonconcurrently and concurrently randomized participants who could not have been randomized to the drug should not be included.” to clarify intent.
III.C	321-355	The guidance appropriately identifies concerns regarding post-randomization substudy consent and the potential for introducing bias. However, it does not provide practical recommendations for addressing the participant burden associated with increasingly lengthy and complex master protocol consent forms.	Request FDA provide additional guidance and examples of acceptable approaches to support a simplified consenting process and reduce consent burden without introducing bias.
III. E	427 - 440	The guidance discusses conducting the analysis separately for each drug-specific substudy. To maintain operational efficiency and blinding, IAs should be conducted at the same calendar time for all available drugs in the platform. The timing of IA should be based on calendar time, not information, using the corresponding error spending function for each comparison.	Suggest the Agency add the following recommendation: To maintain operational efficiency and blinding, IAs should be conducted at the same calendar time for all available drugs in the platform as the timing of IA should be based on calendar time, not information, using the corresponding error spending function for each comparison.
III. F	452	The guidance mentions comparisons between drugs, however, there may be confounding factors to be addressed in between drug comparisons.	Recommend FDA add: “Sponsors planning on conducting these comparisons should prespecify them in the statistical analysis plan, along with methodology to handle possible confounders.”
III. G	511 - 520	It appears that the considerations of separate analyses vs. borrowing effects across populations are here repeated in total 3 times within one section (starting at the beginning of the section, and twice in the lines listed)	Recommend the Agency shorten the section and avoid duplication of the same message. Suggested tructure should be improved to avoid jumping: 1.) Intro on Basket trials 2.) Definition of primary objective 3.) Alignment in evidentiary strategy 4.) Analysis methods 5.) Justification 6.) Bias/Variance tradeoff and benefit-risk 7.) Operating Characteristics
III. H	532 - 536	The guidance mentions evaluating operating characteristics but does not describe different scenarios.	Suggest FDA provide in the appendix of illustrative examples of simulation scenarios for platform trials and analyses approaches, including heterogeneous treatment-effect and temporal-drift scenarios.

III. H	583 - 589	The guidance discusses borrowing across substudy populations but does not explicitly discuss evaluation of false-positive operating characteristics when treatment effects differ across populations.	Suggest FDA further discuss evaluation of false-positive operating characteristics when information is borrowed across substudy populations, particularly in scenarios where true treatment effects differ between populations.
IV	650 - 668	The guidance discusses dissemination of results which is a key point of relevance. Unfortunately, clear guidance on how to mitigate this practical concern is not provided. Clearer guidance on best practices would be desired.	Request FDA provide examples for best practices, instead of just spelling out the concern. For example, there could be considerations on conducting joint interim analysis across all substudies with alpha-spending rules and provide best practices to minimize unblinding when reporting one trial vs. another.
V	706-707	Original text: "The master protocol sponsor should request a pre-IND meeting to discuss the protocol and submission details." The guidance should recognize that pre-IND meetings for master protocols should generally be recommended when the master protocol is intended to generate substantial evidence of effectiveness. Pre-IND meetings could be encouraged, but are not necessary when the master protocol is designed to generate early phase data.	We recommend the following revision: "The master protocol sponsor should request a pre-IND meeting to discuss the protocol and submission details, specifically when the master protocol is intended to contribute to substantial evidence of effectiveness."
V.A	728-733	The guidance provides considerations to support regulatory review and provides an eCTD of an IND with master protocol and substudies (Figure B); however, further clarification of master protocol document structure would be beneficial. Additionally, the guidance addresses eCTD organization but does not fully address clinical study reporting strategy.	FDA should consider providing a sample master protocol table of contents or modular document framework that distinguishes content expected in the overarching master protocol versus substudy-specific appendices, drug-specific sections, statistical appendices, operational manuals, and safety plans. This would support consistency in authoring, review, amendment management, and submission organization. For the CSR, FDA should clarify whether sponsors should generally prepare one integrated CSR, separate substudy CSRs, a modular CSR with substudy-specific sections, or staged CSRs when substudies complete at different times. This is important planning, submission readiness, and long-term document lifecycle management.
V. C	793-842	The guidance defines regulatory procedures for master protocol amendments. Additional guidance regarding operational implementation of changes may be helpful given the complexity of managing updates across multiple substudies, sites, countries, vendors, and participant-facing documents.	Request FDA provide additional guidance on operational implementation of master protocol amendments, including informed consent updates, site training, and coordination of changes across participating sites and substudies, SAP update, and cross-reference notification(s).