November 28th, 2018

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

Re: Docket No. FDA-2018-D-3292: Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics; Draft Guidance for Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance on Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics.

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 members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

This Draft Guidance provides important information to allow companies to use master protocols and is welcomed by our members. The clinical sections are well-covered, however, the statistical sections lack completeness and clarity. For example, information critical for controlling for type I error in Master Protocols appears to be missing from this draft guidance. The full potential of a confirmatory master protocol trial can only be realized with consensus on type I error control. We have provided comments below to address this issue that we hope the Agency will consider.

As a general comment, we find that FDA's thinking and expectations for master protocols used in early stage trials versus late stage trials is not fully clear. It would be helpful if FDA would provide further explanation for what should be considered for an early stage trial and, similarly, for a late stage trial, and what would apply to both.

Secondly, BIO believes the Draft Guidance could define the three types of Master Protocol trials that are introduced in Section 1: Basket, Umbrella, and Platform. In addition, it would be beneficial to add a description of platform trials under Section IV, as it was done for basket and umbrella trials. For reference, we would suggest the definitions included in Janet

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

Woodcock's 2017 publication, "Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both"[1].

Furthermore, the Draft Guidance should provide additional clarification over certain master protocol design specifications such as in the disease areas where multiple acceptable standards of care (SOC) are available for the studied population, would the agency agree that one investigational arm may be compared to two different control arms? In addition, the Draft Guidance should provide additional information around how to handle a master protocol with sub-studies which will form a basis of a marketing application (i.e., phase 3 trial).

BIO appreciates this opportunity to submit comments on the Draft Guidance on Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

[1] http://website.aub.edu.lb/sharp/Publications/Master-Protocols-to-Study-Multiple-therapies.pdf

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
General	While this guidance provides recommendations of master protocol application in oncology drug/biologics development, its key principles are applicable to broader drug development.	Suggest FDA expand the scope of this guidance to cover non-oncology drug/biologics product development.
Lines 20-22	The Draft Guidance should provide additional clarity on RP2D.	BIO suggested edit: "In general, the recommended phase 2 dose (RP2D) has been established for an investigational drug or each of the investigational drugs evaluated in the master protocol but may not have been established for the drug combination(s)."
II. BACKGROUND		
III. MASTER PROTOCOL DEFINITION AND POTENTIAL OPPORTUNITIES AND CHALLENGES		
A. Description and Concept of Master Protocols		
Lines 74-77	The threshold and distinction between a limited multi-cohort Phase 2 signal-seeking trial versus a basket trial that would be governed by a Master Protocol/Master Protocol IND is not clear. Moreover, usually it is not necessary to perform multiplicity adjustment across studies. Under the framework of "master protocol," it would be helpful to clarify in the guidance that multiplicity adjustment is not expected across substudies/cohorts.	BIO suggested change: "For the purpose of this guidance, a master protocol is defined as a protocol designed with multiple substudies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure. Multiplicity adjustment is not required across substudies in a master protocol." FDA also should provide additional clarity on the distinctions between a limited multi-cohort Phase 2 signal-seeking trial versus a basket trial (Master Protocol) in the final version of the guidance.
Lines 77-79 and Lines 118-121	It is unclear what would be required before evaluation of non-oncology drugs in a master	If the guidance is expanded to included non-oncology drug development, suggest that FDA clarify the requirement for establishing the RP2D non-cancer drugs.

SECTION	ISSUE	PROPOSED CHANGE
	protocol. Does the preliminary dose-finding First in Human (FIH) trial needed to be in patients?	
B. Potential Opportunities and Challenges Posed by Master Protocols		
Line 100	There are a number of key challenges which should also be recognized in the Draft Guidance, these include: (i) Estimating treatment effect in the master protocol setting is less well studied in the current literature; (ii) Operational difficulty with safety regulatory reporting requirements; and (iii) the operational complexity, more intense trial planning and more frequent interactions with regulatory agencies.	FDA should consider including the afore mentioned challenges in this section as well as reference them throughout the document as appropriate. In addition, the Agency should consider providing recommendations/best practices on how to address these challenges.
Line 102	The challenges listed here are not limited to Master Protocol trials. In general, it is not easy to attribute adverse events to one or more investigational drugs when study involves combination drugs in testing.	BIO suggested adding the following challenge: "As with other studies that involve combination drugs in testing, difficulty in attribution of adverse events to one or more investigational drugs can occur when multiple drugs are administered within various arms and the trial lacks a single internal control for those drugs"
Line 106	We believe that this challenge is more relevant to drugs studied in multiple protocols due to the number of confounding factors, but not necessarily drugs studied in a Master Protocol.	Recommend clarifying this point or removing this as a challenge of Master Protocols.
Line 110	The challenges listed here is not limited to Master Protocols. The potential overestimation of biomarker-drug effect is possible when proper Type-1 error is not controlled.	Suggest clarifying that this challenge is not necessarily specific to Master Protocols or delete from this section.
Line 112	FDA indicates that the presence of multiple study groups allows potential overinterpretation of findings. Additional detail would be useful.	Please provide guidance addressing the problem of multiple comparisons. Can it be described how this issue was addressed in

SECTION	ISSUE	PROPOSED CHANGE
		each of the example protocols provided (i.e. LUNG-MAP, NCI-MATCH)?
Lines 100-113	While the list of potential challenges is not intended to be exhaustive, it may be worth mentioning (either here or later) that between-group comparisons (such as to a common control) will be confounded by time if the groups being compared aren't participating in the study at the exact same time.	FDA should consider mentioning (either here or later in the guidance) that between-group comparisons (such as to a common control) will be confounded by time, if the groups being compared aren't participating in the study at the exact same time.
IV. TYPES OF MASTER PROTOCOLS		
Lines 123-125	It is unclear what method (e.g., formal meeting) should be used to "seek FDA advice." It is also unclear whether a Sponsor should meet with the Agency when new substudies for new combinations or disease subtypes are added to the study.	FDA should provide additional clarity on how to seek advice from the Agency. In addition, it should consider adding a cross reference from this section to section XI where it refers to communicating with FDA.
A. Single Investigational Drug or Investigational Drug Combination Across Multiple Cancer Populations		

SECTION	ISSUE	PROPOSED CHANGE
Line 133 & Lines 164-165	We would like to request clarification to the concepts that a certain study design is "commonly referred to as a basket trial," and "commonly referred to as umbrella trials," based on the following examples: Consider that, IF… • Basket trial=1 drug, multiple indications • different biological characteristics in same tumor determining therapy (eg NSCLCKALK mut vs wt being treated with different drugs)= multiple indications=basket trial • biology determining therapy defines indication (eg MSIhigh prostate and MSIhigh CRC treated with pembro are 1 indication) THEN: 1. a study with multiple MSIhigh tumors treated with same drug is not a basket but a regular study 2. the Lung MAP study, testing multiple drugs in multiple biologically determined indications is not an umbrella study but a "platform/complex" study	We request that FDA provide clarification around these distinctions, keeping in mind these examples.
Lines 136	It is unclear whether future subtypes would also be included as a dotted box in Figure 1 similar to future treatment arms used in Figure 2.	Please provide clarity
Lines 147-148	Innovative Bayesian dose finding methods utilizing dose-limiting toxicity data across subpopulations can be used to improve the efficiency (both operational and statistical) in identifying the MTD or RP2D of the investigational drug in each subpopulation.	Please include comments that such dose-finding components can be included in a basket trial, and further comment on pooled efficacy analysis across substudies in the basket trial.

SECTION	ISSUE	PROPOSED CHANGE
Lines 147-149	This statement, although true, isn't unique to basket trials; the same concept would apply if the substudy were a traditional stand-alone study with sample size re-estimation.	BIO suggested edit: "As with a traditional stand-alone study with sample size-estimation, a strong response signal seen in a substudy may allow for expansion of the substudy to generate data that could potentially support a marketing approval."
Lines 150-152	Regarding "Each substudy should include specific objectives…", the premise of a basket design is that data across substudies may be pooled on the basis of a common biomarker for patient selection. Proper pooling of substudies can further increase efficiency of basket study design. Further, most basket trials are single arm studies, but we believe the guidance should be forward looking and gold-standard randomized designs also should be included. In addition, the required sample size for a disease type depends on the event rate expected for that specific disease and the effect that we want to detect. Sample size should be pre-specified to control the type I error rate for each disease type.	BIO recommends including the following language: "Each substudy should include specific objectives, the scientific rationale for inclusion of each population, and a detailed statistical analysis plan (SAP) that includes sample size justification and stopping rules for futility, for each disease type respectively. For basket designs, sub-studies may be pooled on the basis of a common biomarker for patient selection, to increase efficiency of the study. In addition, basket trials may be randomized, with each substudy having its own control arm and, in this case the overall Type I error should be properly controlled, and details provided in the SAP."
Line 152	The document states that stopping rules for futility are required for each substudy. Stopping rules for efficacy should be mentioned as well (even if efficacy stopping rules are not required).	Consider mentioning stopping rules for efficacy.
B. Investigational Drugs or Investigational Drug Combination(s) in Single Cancer Type		

SECTION	ISSUE	PROPOSED CHANGE
Lines 165-167	FDA please clarify if this text in Line 165-167 can also apply to the Basket design. "Substudies within umbrella trials can include dose-finding components to identify safe doses of an investigational drug combination before proceeding with an activity-estimating component." As BIO believes that umbrella safety lead-ins should also be acceptable for Basket trials designs.	BIO suggested edit: "Substudies within umbrella trials can include dose-finding components to identify safe doses of an investigational drug combination before proceeding with an activity-estimating component. In addition, umbrella safety lead-ins should also be acceptable for Basket trials designs."
Lines 165 – 168; Line 242-249	The concept of allowing dose-finding components is first expressed within the "umbrella trial" description, then in the overall "specific design considerations," which applies to all study types.	To avoid confusion, we suggest that FDA remove the reference to dose-finding from the "umbrella trials" paragraph and retain it only in the "specific design considerations" paragraph.
C. Other Trial Designs		
Lines 214-229	BIO believes that comparative analyses should not be limited to only test and the control arm, but also between experimental arms.	FDA should clarify that comparative analyses between experimental arms is allowed.
Lines 203	Limited detail is provided on designs which incorporate both basket and umbrella features.	FDA should consider including further comment on these complex designs, with a schematic, e.g., NCI ALK Master Protocol.
V. SPECIFIC DESIGN CONSIDERATIONS IN MASTER PROTOCOLS		
A. Use of a Single Common Control Arm		
Lines 219-220	It is unclear whether a common control arm can be used for similar diseases (e.g., subtypes of soft tissue sarcoma). And whether it is also possible to use a new arm if added at a later date which randomizes to the common control arm (i.e., not all patients in the control arm would have been contemporaneously enrolled with the new investigational arm).	FDA should provide additional guidance on how to approach the afore mentioned cases.

SECTION	ISSUE	PROPOSED CHANGE
Line 221-223	It is unclear how data analysis under the scenario where the SOC changes during the trial conduct would be performed.	FDA should provide clarification, in particular as to how the control arm would be analyzed, how to replace control arm patients enrolled and treated and when to pool patients enrolled and treated under the previous SOC with patients enrolled and treated with the new SOC.

Lines 221-225	The draft guidance states: *Changes in SOC for the target population can occur during the conduct of the trial, because of either a new drug approval or new scientific evidence, making it no longer ethical to randomize patients to the previous SOC. In that case, the sponsor should suspend patient enrollment until the protocol, the SAP, and the protocol informed consent document are modified to include the new SOC as control.* The Draft Guidance is not clear on how to operate in case an approved drug is not really used as standard of care (e.g., romidepsin/ belinostat/ pralatrexate are approved for PTCL but NCCN guidelines recommend to offer patients experimental therapies rather than the approved drugs; or, a drug approved in a different indication may become SOC per NCCN guidelines if a phase 2 is positive in the indication being studied). Changing the control during the conduct of trial could be operationally and statistically difficult. For example, a study with 20 patients per cohort may have enrolled already 15 per cohort by the time the new SOC is approved/established. Suspending patient enrolment to change control for the last 5 patients would delay study completion and not really allow a fair control comparison, as 5 out of 15 patients in the control arm would receive a drug more effective than the one used as a control in 15 out of 20 patients. Since in this scenario the new drug has been just approved, and a clear randomized study result is presumably available, wouldn't it make sense to just	Please clarify in the final guidance.

SECTION	ISSUE	PROPOSED CHANGE
	remove the control arm and compare to the newly obtained results? The other option would be to continue with the current design, and re-enroll the entire control arm (e.g., 20 patients). However, this would also bring a big complication if most of patients in the other arms have been randomized already because subsequent enrolment would be unbalanced.	
Lines 223-225	If the control needs to be changed during the conduct of the trial due to a new SOC available, this will create challenges with data interpretation in the analysis due to the mixed control data and study design with a new SOC.	Please provide comments on statistical considerations for change of control due to a new SOC and add this information to Section VII "Statistical Considerations." Please also clarify if change of control due to a new SOC available would apply to Section V. B.
Lines 223-225	SAP modification should not be a determining factor here. The enrollment can be resumed as long as the protocol and the protocol informed consent document are modified.	FDA should consider removing "the SAP" from this sentence.
Line 228	Based upon objectives of the trial, there may be other comparisons between experimental arms that may be appropriate.	Please provide an additional comment regarding this issue
B. Novel Combination of Two or More Investigational Drugs		

SECTION	ISSUE	PROPOSED CHANGE
Lines 242-249	FDA should make recognition of other data sources outside Clinical Trials.	BIO suggested edit: "Proposed Change: Safety data from a minimum of six patients treated at the proposed dosage for the drug combination regimen should be available, either from the current study or from data in the literature, before proceeding with the efficacy evaluation."
Lines 246-248	*"..sponsors should ensure that the full relevant age range of pediatric patients is covered and the investigational drug provides the prospect of direct clinical benefit to pediatric patients.."* This means requiring a prior dose-ranging study in all pediatric age groups, especially when there is no relevant animal model for an age group, delaying the time when the drug is brought to phase 2 in children.	BIO suggested change: "..sponsors should make every effort to ensure that the full relevant age range of pediatric patients is covered and the investigational drug provides the prospect of direct clinical benefit to pediatric patients.."
Lines 248-249	There are cases where it is appropriate for a Sponsor to proceed with the efficacy phase without submission of the dose-finding results for FDA review. In addition, it is unclear what the mechanism of interaction would be.	BIO recommends FDA include more specific recommendations for when this FDA review of dose-finding results would be desired. In addition, FDA should provide more specific guidance on the mechanism of interacting with the Agency in this instance as well as an expected timeframe throughout the process.
Lines 248-250	If no safety signals precluding study continuation have been observed during the dose-finding phase, the study should not be unnecessarily paused for a formal review of the data.	BIO suggested edit: "The sponsor should submit results of the dose-finding phase for FDA review ~~**before proceeding with the efficacy phase."**~~
Lines 252-254	It would be helpful for FDA to clarify that (if) each drug contribution is to be assessed against control.	BIO suggested edit: "it is essential that the general investigational plan describe the approach to demonstrating the contribution of each investigational drug to the observed treatment effect to support a risk-benefit assessment, against the common control arm"
C. Studies With Drugs Targeting Multiple Biomarkers		

SECTION	ISSUE	PROPOSED CHANGE
Lines 265-266	FDA's thinking on multiplicity adjustment for subgroup analysis in master protocols is not clear.	Please provide FDA's current thinking on multiplicity adjustment, particularly addressing master protocols as described in Section IV. A.
D. Adding and Stopping Treatment Arms		
Lines 274-280	The prevalence of biomarker positive patients in the overall population is lower than the natural prevalence. Similar issues may arise for overlapping populations. One example to illustrate this point is: Two investigational treatments tested in an umbrella trial, with one agent for biomarker positive patients, and the other for all comers, and both arms share a common control treatment.	BIO suggested change "(…) experimental arm based on futility rules. Protocols should consider whether the approach of assigning patients with more than one biomarkers of interest would impact the prevalence of the biomarkers in each subpopulation and whether any statistical methods to adjust this potential issue/bias are needed."
Lines 277	The finalization of the SAP covering these circumstances prior to initiation of the trial is complex.	Recommend that draft SAP should be acceptable prior to trial initiation.
Lines 279	Need for type I error control if sample size will be re-estimated in multiple treatment arms is not clear.	Please provide additional guidance in Section VII. C.
E. Independent Data Monitoring Committee		
Lines 282-298	While for placebo-controlled studies it is customary to ask an IDMC to oversee both safety and efficacy of the study, for Phase 1 studies, when present, the IDMC usually oversees primarily safety. In open-label master studies, Sponsor and IRB/Investigators may define in the charter if the IDMC has a primary responsibility on safety only, or safety and efficacy oversight.	FDA should provide further clarity.

SECTION	ISSUE	PROPOSED CHANGE
Lines 284-286	Not all studies to support a marketing application require independent radiological review (IRC), for example, an umbrella trial with OS as the primary endpoint.	BIO suggested edit: "If results from one or more substudies are anticipated to form the basis of a marketing application, based on tumor response(…)"
Lines 288-291	In the case when IDMC recommends protocol modifications or other actions based upon ad hoc assessments of efficacy, there are potential issues with the sponsor's maintenance of trial integrity.	Please describe FDA's current thinking on what it means by trial integrity as well as how to maintain it in this context.
Line 296	The level of blinding/unblinding required for such committees could be detailed more	Please provide additional detail on blinding/unblinding for the IDMC
Lines 293-295	It may not be advisable for risk-benefit evaluation during the trial to have two separate independent committees in place, one with access to efficacy and the other to safety. We believe that only 1 committee should be tasked with reviewing study data.	BIO suggested edit: "The responsibilities of the IDMC can be limited to assessment of efficacy with another committee responsible for the assessment of safety (e.g., an independent safety assessment committee (ISAC)). However, the IDMC can also be structured to perform both safety and efficacy functions in the context of a risk/benefit assessment."
VI. BIOMARKER DEVELOPMENT CONSIDERATIONS		
Lines 304-308	There is quite a bit of analytical data that is generated during development of an IVD and/or Clinical Trial Assay, and there could be confusion as to what data would support investigational use.	BIO suggested edit: " Protocols with IVD tests that are not analytically validated can be placed on clinical hold for deficiencies in design to meet the stated objectives. **Sponsors can contact CDRH directly with questions relating to analytical validation of the investigational IVD.**"
Lines 311-313	It is unclear how and when Sponsors should submit IVD analytical data to FDA.	FDA should consider providing additional guidance on this issue.
VII. STATISTICAL CONSIDERATIONS		

SECTION	ISSUE	PROPOSED CHANGE
Lines 329	The recent draft guidance "Adaptive Designs for Clinical Trials of Drugs and Biologics" provides more statistical detail, and this level of statistical detail for different types of designs used in master protocols would be beneficial.	Please provide additional details in Section VII.
Lines 329	The recent draft guidance "Adaptive Designs for Clinical Trials of Drugs and Biologics" provides more statistical detail, and this level of statistical detail for different types of designs used in master protocols would be beneficial. Although ICH E9 is referenced in this document, issues with multiplicity is not addressed in this guidance.	Please provide additional details in Section VII. Specific considerations might include whether there should be family-wise alpha control for multiple primary statistical testing. If yes, should there be a penalty for using such a master design?
A. Nonrandomized, Activity-Estimating Design		

Lines 329-344	It would be helpful to have agency guidance regarding Type I error rate considerations for master protocols with exploratory or confirmatory intent. The issue on Type I error rate control for master protocols is unique. A clear guidance on trials with confirmatory intent will save the time on designing these trials and make the regulatory approval decision more predictable in the end.	BIO suggests adding a new section here after Section D: "Section E. Type I Error Rate Considerations Master protocols may be exploratory or confirmatory. For exploratory master protocols, Type I error should be considered in the context of hypothesis generation. For confirmatory master protocols, • Non-randomized designs: Sometimes it may be challenging to estimate historical control response rate precisely. In such situation, Type I error rate can be difficult to interpret. Whenever available, real world evidence in the same patient population may be used to assist with interpretation. See Section VII, A. • Randomized designs: ○ For basket trials, Type I error rate for the global null hypothesis (i.e., the drug is inactive in all populations) should be controlled at the 1-sided 2.5% level, for example, using the pruning and pooling method [1, 2]. Possible heterogeneity in treatment effect across remaining tumor indications in the pooled population is an issue, similar to the impact of baseline characteristics on treatment effect in conventional Phase 3 trials. Regulatory decisions on drug approval or the scope of the label hinge upon the totality of data, post a statistically positive study. For platform trials, in general, if the experimental arms are put together in a single trial because the corresponding research questions are related (e.g., several doses/schedules of one treatment), multiplicity adjustment should be made. However, if the experimental arms are several different treatments and they

SECTION	ISSUE	PROPOSED CHANGE
		share a common control in a master protocol for the purpose of improving efficiency, the interpretation of the results of one comparison (experimental vs. control) has no direct bearing on the interpretation of the others. In this situation, multiplicity adjustment is not required (i.e., each comparison can be tested at the 1-sided 2.5% level for a confirmatory trial) [3].” 1. Beckman RA, Antonijevic Z, Kalamegham R, Chen C. Design for a basket trial in multiple tumor types based on a putative predictive biomarker. Clinical Pharmacology & Therapeutics 2016. DOI:10.1002/cpt.446. 2. Chen C, Li N, Yuan S, Antonijevic Z, Kalamegham R, Beckman RA. Statistical design and considerations of a Phase 3 basket trial for simultaneous investigation of multiple tumor types in one study. Statistics in Biopharmaceutical Research 2016; 8 (3): 248-257. DOI: 10.1080/19466315.2016.1193044. 3. Freidlin B, Korn EL, Gray R, Martin A: Multi-arm clinical trials of new agents: some design considerations. Clin Cancer Res 2008, 14:4368–4371
Lines 333-335	While using the 95% CI is important for studies aiming at accelerated approval, it is limiting the flexibility of initial proof of concept, signal-generation studies, where 90% CI could be acceptable. It is understood, however, that if data from a POC/signal-generation study want to be used for accelerated approval, the study should be amended to enroll a sample size adequate to control a type I error at 5%.	BIO suggested edit: “In nonrandomized protocols, where the primary endpoint is ORR, the planned sample size should be sufficient to rule out a clinically unimportant response rate based on the lower bound of the 95 percent confidence interval around the observed response rate, if it is used to support accelerated approval.”

SECTION	ISSUE	PROPOSED CHANGE
Line 335	For exploratory studies, the confidence interval may not need to be held at the 95% level.	BIO suggested edit: "In nonrandomized protocols, where the primary endpoint is ORR, the planned sample size should be sufficient to rule out a clinically unimportant response rate based on the lower bound of an appropriate ~~the 95 percent~~ confidence interval around the observed response rate."
Line 336-337	Recommendation for Simon two-stage design should be expanded to include other potential designs. Determination of anti-tumor activity could be assessed using other approaches such as Bayesian statistical framework which is especially attractive in expansion cohort with low sample size. Moreover, Bayesian paradigm lends itself quite naturally to the implementation of interim analysis to trigger, for example, early stopping of the trial due to lack of activity.	Please also include other adaptive designs and Bayesian designs in this recommendation. For example: "FDA recommends designs such as the Simon two stage or Bayesian design that limit exposure to an ineffective drug. It also would be helpful if FDA could share its position on basket design with information borrowing across cohorts within the same trial. If multiple diseases are studied in one basket trial using the same primary endpoint, is there any recommended method to borrow information from the other disease types to make claim of efficacy for one disease type, if there is a common factor (eg a mutation that makes tumor sensitive to the drug being tested)? What are the criteria for the information borrowing?
Lines 342-344	It is not clear what "major advance" refers to here.	It would be helpful for to clarify with examples what it would consider as "major advance" in this context.
B. Randomized Designs		
C. Master Protocols Employing Adaptive/Bayesian Design		

SECTION	ISSUE	PROPOSED CHANGE
Lines 357	Bayesian statistical method could also be used to modify the randomization ratio for ethical reasons, as response adaptive randomization is commonly used in the master protocol.	BIO suggested edit: "Master protocols can use a Bayesian statistical method or other methods for planning or modifying the sample size, modifying the randomization ratio, dropping an arm, or other adaptive strategies." Additional recommended reference: J. Lin, V. Bunn. (2017) "Comparison of multi-arm multi-stage design and adaptive randomization in platform clinical trials". *Contemporary Clinical Trials,* Volume 54, 48-59
D. Master Protocols With Biomarker-Defined Subgroups		
Line 370	Assigning patients with multiple biomarkers to one biomarker group that has the highest predictive value or assigning based upon a prespecified randomization ratio such as a reversed ratio of prevalence rates have been debated amongst the research community.	BIO suggest removing or replacing with another example that is not as controversial
VIII. SAFETY CONSIDERATIONS		
A. Safety Monitoring and Reporting Plans		
Lines 390	In practice, whenever drug safety issues occur, the study team needs to query the data to verify the validity of the event and the causes and time that it occurred, which takes time.	FDA should consider removing "rapid" as this may not be a practical request
B. Independent Safety Assessment Committee		
General	In this section FDA recommends that all master protocols should have an independent DMC or safety review committee; this seems to be rather extreme if applied in all cases.	The use of an IDMC should be dependent on the design of the clinical trial (designed with registration intent vs. exploratory), and whether a safety committee is felt to be needed. Just as Sponsors may elect not to use an IDMC in a Phase 2 study, Sponsors ought to have the same flexibility with master protocols. FDA should revise the guidance accordingly.

SECTION	ISSUE	PROPOSED CHANGE
General	The guidance does not discuss blinding for master protocols	FDA should add recommendations or descriptions of situations in which blinding in a master protocol would be expected, useful or unnecessary/not feasible.
Lines 405-407	It is unclear if the recommendation for an ISAC is to be constituted with members external to the Sponsor's organization	BIO believes that an ISAC could be an independent group internal or external to the Sponsor's organization.
Line 405-411	We understand the importance of safety data monitoring, especially in the context of Master protocols, given their complexity. However, these trials can generate an enormous amount of safety data which can pose many challenges in interpretation. It is suggested that an IDMC should only be required for some trials, based on their complexity including: therapeutic index, the number of different cohort objectives, or size of trial populations.	BIO suggested edit: "For all master protocols, the sponsor should consider establishment of an ISAC or an IDMC structured to assess aggregate safety data in addition to efficacy, based on the study design complexity of these trials including therapeutic index; size of the trial population(s), and the number of different cohorts. The ISAC or IDMC may be comprised of internal or external members, or a mixture of both. The sponsor should describe in the IND the constitution of this committee and the definition of its responsibilities. The committee should ~~complete the real-time review of all serious adverse events as defined in FDA regulations and periodically~~ ~~assess the totality of safety information in the development program.~~ meet periodically to assess the totality of safety information in the development program.29 The ISAC or IDMC should have responsibility for conducting prespecified and ad hoc assessments of safety to recommend protocol modifications or other actions including but not limited to the following:
Lines 406-407	Inclusion of IDMC/ISAC constitution and responsibilities in the IND is not overly clear.	Please clarify the acceptability of IDMC constitution and responsibilities within the protocol, rather than as a specific submission to the IND.
C. Institutional Review Board/Independent Ethics Committee		

SECTION	ISSUE	PROPOSED CHANGE
Line 436-438	It is unclear what specifically is expected during the annual safety assessment. Sponsors currently do an annual DSUR that includes SAE data only, but this report does not go to investigators. Sponsors also prepare SAE line listing reports that go to IRBs/ERBs and investigators twice per year. AE data is not included in the DSUR or SAE Line Listings. Study teams typically will conduct regular Trial Level Safety Reviews, which will include AE data, but this information is not typically provided to the investigators.	FDA should provide additional information as to what specifically is to be included in the "assessment of safety" and the frequency of this assessment. BIO suggest that the trigger for providing this assessment could eb based on study enrollment rather than specific timepoints.
D. Informed Consent Document		
Line 475-486	Considerations for substudy/cohort ICFs versus an ICD that covers the Master Protocol in its entirety is not clear.	Please provide more specific recommendations regarding the expectations of the ICD, and whether separate consents are required for the master protocol and the substudies.
IX. ADDITIONAL REGULATORY CONSIDERATIONS		
Lines 489-501	When a first indication is pursued for registration based on results from a basket trial, it should be based on the first IND; sponsors should open a second IND for a subsequent indication to be pursued.	FDA should clarify/ expand on this point.
X. CONTENT OF A MASTER PROTOCOL		
A. New IND Submission		
General	The IND process for a master protocol including two novel-novel combinations (A+B, A+C) has not been included.	Please clarify whether in the presence of two novel-novel combination (A+B, A+C) in the master protocol, the sponsor should submit separate IND applications before initiating dose finding components.

SECTION	ISSUE	PROPOSED CHANGE
Lines 542	FDA is suggesting that the "The proposed informed consent document" be included in the master protocol by the placement of this bullet in Line 542. Currently ICH guidance does not include ICFs within the protocol or protocol appendices.	BIO suggest moving this text above line 529 so that the informed consent document draft for the investigation is included in the IND submission with the protocol not as part of the protocol as the current placement suggests. Also note that substudies of the master protocol may have different informed consent documents so this may need to be clarified.
B. Amendments to the Master Protocol		
Lines 561-566	In general, to facilitate communications and expedite the drug development program, FDA recommends that a sponsor submit a substudy for disease-specific development to a new IND reviewed by the appropriate disease-specific team, particularly when that team is located in another review division. In such instances, the sponsor should cross-reference to the original IND information on common elements (e.g., description of groups responsible for monitoring patient safety) rather than resubmit the information with the substudy.	Please clarify further the administrative or operational processes that FDA will use when a master protocol study results in multiple INDS—disease-specific and/or across different review divisions. FDA should also describe the communications that might take place between the original review team and the new review team to avoid different/inconsistent recommendations.
XI. COMMUNICATION AND INTERACTIONS WITH FDA		
Line 500	It is unclear how a Sponsor should communicate an IVD to CDRH and the timing in relation to an IND.	FDA should provide further information on communication and interactions.
APPENDIX		
Lines 621	BATTLE-1 trial is also a good example of a complex master protocol.	Consider inclusion of BATTLE-1 as described in lines 368-370 in the examples for the Appendix.