Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Procedural

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Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Cancer Drugs and Biologics Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to sponsors of drugs or biologics for the treatment of cancer regarding the design and conduct of clinical trials intended to simultaneously evaluate more than one investigational drug[2] and/or more than one cancer type within the same overall trial structure (master protocols) in adult and pediatric cancers. In general, the recommended phase 2 dose (RP2D) has been established for an investigational drug or drugs evaluated in a master protocol.

This guidance is intended to serve as advice and a focus for continued discussions among FDA, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance describes aspects of master protocol designs and trial conduct and related considerations, such as biomarker codevelopment and statistical analysis considerations, and provides advice on the information that sponsors should submit to FDA and on how sponsors can interact with FDA to facilitate efficient review.

This guidance does not cover FIH clinical trials using expansion cohorts to expedite drug development. FDA addresses that topic in the draft guidance for industry *Expansion Cohorts:*

[1] This guidance has been prepared by the Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research in cooperation with the Oncology Center of Excellence and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purpose of this guidance, the term *drug* refers to human drugs and biological products.

[3] In addition to consulting guidances, sponsors are encouraged to contact the review division to discuss specific issues that arise during drug development.

Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics.[4]

This guidance does not address all issues relating to clinical trial design, statistical analysis, or the biomarker development process. Those topics are addressed in the International Conference on Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials* and the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices.*[5]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

There is increased interest in expediting late-stage drug development through developing trial designs that test multiple drugs and/or multiple cancer subpopulations in parallel under a single protocol, without a need to develop new protocols for every trial. The term *master protocol* is often used to describe the design of such trials, with variable terms such as *umbrella*, *basket*, or *platform* describing specific designs. Examples of trials using master protocols include the Lung-MAP trial (NCT02154490), the NCI-MATCH trial (EAY131, NCT02465060),[6] [see Figures B and C in the Appendix], and the Pediatric MATCH trial (APEC1621, NCT03155620)] In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, master protocols use a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple substudies, allowing for efficient and accelerated drug development.

Because of the complexity of these trials evaluating multiple drugs and/or disease populations and the potential regulatory impact, it is important that such trials be well designed and well conducted to ensure patient safety and to obtain quality data that may support drug approval.

[4] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[5] See also the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* and the draft guidances for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* and *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, these guidances will represent the FDA's current thinking on these topics.

[6] See information on this trial at the National Cancer Institute web page at https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCT02465060&r=1.

III. MASTER PROTOCOL DEFINITION AND POTENTIAL OPPORTUNITIES AND CHALLENGES

A. Description and Concept of Master Protocols

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. In general, FDA strongly recommends that the sponsor establish the RP2D for the investigational drug(s) before evaluation using a master protocol. Individual drug substudies under the master protocol can incorporate an initial dose-finding phase, for example, in pediatric patients when sufficient adult data are available to inform a starting dose and the investigational drug provides the prospect of direct clinical benefit to pediatric patients.[7]

A master protocol may be used to conduct the trial(s) for exploratory purposes or to support a marketing application and can be structured to evaluate, in parallel, different drugs compared to their respective controls or to a single common control. The sponsor can design the master protocol with a fixed or adaptive design[8] with the intent to modify the protocol to incorporate or terminate individual substudies within the master protocol. For examples of types of master protocols, see section IV., Types of Master Protocols.

B. Potential Opportunities and Challenges Posed by Master Protocols

The potential advantage of a master protocol is flexibility and efficiency in drug development, consistent with FDA's goal of helping to make safe and effective drugs and drug combination treatments available to the public. A master protocol provides an opportunity to incorporate efficient approaches, such as a shared control arm and/or the use of centralized data capture systems to enhance efficiency. However, a master protocol also can create challenges in the conduct and analysis of the trial that, if not properly addressed, can increase risk to patients or delay the development of the drug.

Examples of potential challenges include the following:

- 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.

- With multiple drugs being studied across multiple protocols and investigational new drug applications (INDs), assessing the safety profile of any given investigational drug is difficult.

[7] 21 CFR 50 subpart D.

[8] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics.* When final, this guidance will represent FDA's current thinking on this topic.

- The presence of multiple study groups allows potential *overinterpretation* of findings, resulting in delays in drug development. For example, a biomarker-defined subpopulation could be identified, because of multiple comparisons, as a responder population based on ad hoc between-arm comparisons that prove to be false.

IV. TYPES OF MASTER PROTOCOLS

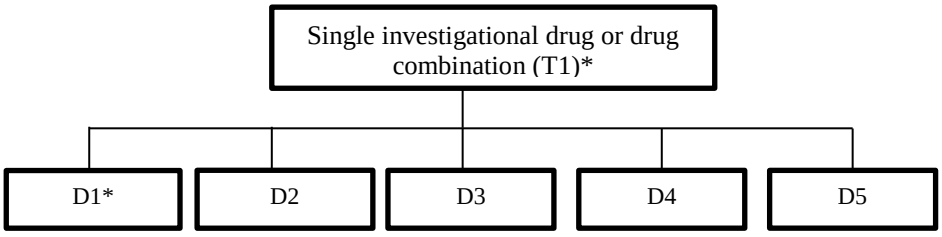
This section provides examples of types of master protocols and considerations related to their designs. FDA strongly recommends that all investigational drugs evaluated in a master protocol undergo preliminary dose-finding FIH trials with the RP2D of each investigational drug established before evaluation in a master protocol.

FDA strongly encourages sponsors to discuss with the review division plans to develop drugs under a master protocol early in the development program to obtain feedback on the design of such a protocol before the submission.

A. Single Investigational Drug or Investigational Drug Combination Across Multiple Cancer Populations

A master protocol designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics is commonly referred to as a *basket trial* (shown in Figure 1).

Figure 1: Schematic Representation of a Master Protocol With *Basket Trial* Design



* T = investigational drug; D = protocol defined subpopulation in multiple disease subtypes.

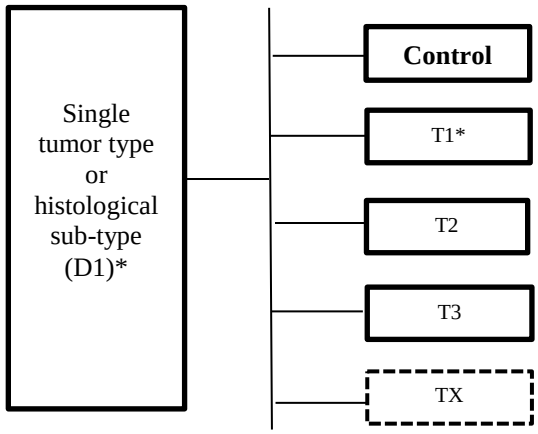
The substudies within basket trials are usually designed as single-arm activity-estimating trials with overall response rate (ORR) as the primary endpoint. A strong response signal seen in a substudy may allow for expansion of the substudy to generate data that could potentially support a marketing approval. 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 specific aspects related to design and analysis related to a master protocol for a basket trial, see sections V., Specific Design Considerations in Master Protocols, and VII., Statistical Considerations.

An example of a master protocol with *basket trial* design is the phase 2 trial evaluating vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations[9] (see Figure A in the Appendix).

B. Investigational Drugs or Investigational Drug Combination(s) in Single Cancer Type

A master protocol designed to evaluate multiple investigational drugs administered as single drugs or as drug combinations in a single disease population are commonly referred to as *umbrella trials* (shown in Figure 2). 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 previously stated, the sponsors should ensure the RP2D for each investigational drug has been established before evaluation in a master protocol.

Figure 2: Schematic Representation of a Master Protocol with *Umbrella Trial* Design



* T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border depicts future treatment arm.

Umbrella trials can employ randomized controlled designs to compare the activity of the investigational drug(s) with a common control arm. The drug chosen as the control arm for the randomized substudy or substudies should be the standard of care (SOC) for the target population, and this may change over time if newer drugs replace the SOC. For specific aspects related to design and analysis related to a master protocol for an umbrella trial, see sections V. Specific Design Considerations in Master Protocols, and VII., Statistical Considerations).

An example of a master protocol with umbrella trial design is the original version of the LUNG-MAP trial,[10] a multidrug, multi-substudy, biomarker-driven trial in patients with advanced/metastatic squamous cell carcinoma of the lung. Eligible patients were assigned to substudies based on their biomarkers or to a *nonmatch* therapy substudy for patients not eligible

[9] Hyman DM et al., 2015, "Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations, N Engl J Med, 373(8):726-736.

[10] Herbst RS et al., 2015, Lung Master Protocol (Lung-MAP)- A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400, Clin Cancer Res,21(7):1514-1524.

for the biomarker-specific substudies. Within the substudies, patients were randomized to a biomarker-driven target or to SOC therapy (see Figure B in the Appendix).

C. Other Trial Designs

Master protocol designs may also incorporate design features common to both *basket* and *umbrella* trials and may evaluate multiple investigational drugs and/or drug combination regimens across multiple tumor types.

An example of a master protocol with a complex trial design is the NCI-MATCH trial,[11] which aims to establish whether patients with one or more tumor mutations, amplifications, or translocations in a genetic pathway of interest identified in solid tumors or hematologic malignancies derive clinical benefit if treated with drugs targeting that specific pathway in a single-arm design (see Figure C in the Appendix).

V. SPECIFIC DESIGN CONSIDERATIONS IN MASTER PROTOCOLS

A. Use of a Single Common Control Arm

FDA recommends that a sponsor use a common control arm to improve efficiency in master protocols where multiple drugs are evaluated simultaneously in a single disease (e.g., umbrella trials). FDA recommends that the control arm be the current SOC so that the trial results will be interpretable in the context of U.S. medical practice. 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.

In general, comparative analyses may be conducted only between a test drug and the common control and not between experimental treatment arms (for statistical considerations in the use of common control, see section VII., Statistical Considerations).

B. Novel Combination of Two or More Investigational Drugs

In master protocols with substudies intended to evaluate concomitant administration of two or more investigational drugs, the sponsor should provide strong scientific rationale for the use of the drug combination regimen. FDA strongly recommends that the sponsor ensures the RP2D has been identified for each individual drug in all cases where each drug may have antitumor activity.

The master protocol should summarize available safety, pharmacology, and preliminary efficacy data for each investigational drug; the biological rationale for use of the drugs in combination rather than use of an individual drug; and evidence, if any, of synergy when used in combination.

[11] Abrams J et al., 2014, National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network, Am Soc Clin Oncol Educ Book:71-6, doi: 10.14694/EdBook_AM.2014.34.71.

In some instances, the master protocol may include a dose-finding component for novel combinations where the RP2D of the combination regimen has not been established. Safety data from a minimum of six patients treated at the proposed dosage for the drug combination regimen should be available before proceeding with the efficacy evaluation. If such an approach is considered in a pediatric population, 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.[12] The sponsor should submit results of the dose-finding phase for FDA review before proceeding with the efficacy phase.

For clinical development programs designed to evaluate combinations of two or more investigational drugs, 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.[13]

C. Studies With Drugs Targeting Multiple Biomarkers

FDA strongly recommends early discussion of biomarker development plans when the sponsor plans to use one or more biomarkers to inform patient selection for trials. For master protocols with drugs targeting multiple biomarkers, it is essential that patient selection tests be analytically validated with well-defined criteria for marker positivity before initiation of the trial.

In master protocols containing substudies with drugs that target multiple biomarkers, the protocol should contain a prespecified plan for allocation of patients who are potentially eligible for more than one substudy. Patient allocation and sample size assumptions for each randomized substudy should take into consideration the potential prognostic implications of specific biomarkers.

For additional information, see section VI., Biomarker Development Considerations and VII., Statistical Considerations.

D. Adding and Stopping Treatment Arms

Master protocols evaluating multiple investigational drugs can add, expand, or discontinue treatment arms based on findings from prespecified interim analyses or external new data.[14]

Before initiating the trial, the sponsor should ensure that the master protocol and its associated SAP describe conditions that would result in adaptations such as the addition of a new experimental arm or arms to the trial, reestimation of the sample size based on the results of an interim analysis, or discontinuation of an experimental arm based on futility rules.

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[12] 21 CFR 50 subpart D.

[13] See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* and the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products.* When final, this guidance will represent the FDA's current thinking on this topic.

[14] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics.* When final, this guidance will represent FDA's current thinking on this topic.

E. Independent Data Monitoring Committee

If results from one or more substudies are anticipated to form the basis of a marketing application, the master protocol should describe and provide the charter for an independent radiologic review committee to perform blinded tumor-based assessments. In addition, the protocol should describe and provide a charter for an independent data monitoring committee (IDMC) to monitor the efficacy results. The IDMC charter should authorize the committee to conduct prespecified and ad hoc assessments of efficacy and futility and recommend protocol modifications or other actions, including sample size adjustment and discontinuation or modification of a substudy based on futility or overwhelming evidence of efficacy.

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)). The IDMC can also be structured to perform both functions. Pediatric expertise should be provided on IDMCs that will review pediatric studies, and an ethicist should be considered for all studies. For additional responsibilities related to safety monitoring, see section VIII.B., Independent Safety Assessment Committee.

VI. BIOMARKER DEVELOPMENT CONSIDERATIONS

Master protocols evaluating biomarker-defined populations should explain why use of the biomarker is appropriate and employ in vitro diagnostic (IVD) tests that are analytically validated. Use of IVDs with inadequate analytical performance characteristics (e.g., precision, accuracy) may produce unreliable results with respect to performance of the drug. Protocols with IVD tests that are not analytically validated can be placed on clinical hold for deficiencies in design to meet the stated objectives.[15]

Sponsors should establish procedures for sample acquisition, handling, and the testing and analysis plans as early as possible in the biomarker development program. The sponsor may need to submit the IVD's analytical validation data for FDA to determine whether the clinical results will be interpretable.

Further, when the trial uses an investigational IVD, the sponsor and institutional review boards (IRBs) should assess what investigational device application[16] requirements apply[17] using the criteria found in 21 CFR 812.2 that address level of risk that the device presents to trial subjects

[15] 21CFR 312.42(b)(2)(ii).

[16] 21 CFR 812.

[17] See the guidance for sponsors, clinical investigators, IRBs, and FDA staff *FDA Decisions for Investigational Device Exemption Clinical Investigations* and the guidance for IRBs, clinical investigators, and sponsors *IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE Is Needed.*

(i.e., significant risk, nonsignificant risk).[18] Sponsors can contact the appropriate center at FDA (the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER)) for the device, or sponsors can submit all information regarding the oncology codevelopment program, including IVD information in the IND submitted to the Center for Drug Evaluation and Research (CDER) or CBER, to seek trial risk determination.[19]

A sponsor interested in pursuing the development of a specific biomarker test for marketing as a device should consult the appropriate center at FDA (CDRH or CBER) responsible for review of the IVD.

VII. STATISTICAL CONSIDERATIONS

A. Nonrandomized, Activity-Estimating Design

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. The analysis plan should describe the futility analyses to be conducted. FDA recommends designs such as the Simon two-stage design[20] that limit exposure to an ineffective drug. If a sponsor anticipates that the results would form the primary basis of an efficacy claim in a marketing application, the clinical protocol and SAP should ensure that collected data are of adequate quality for this purpose. Additionally, the SAP should prespecify the timing of the final analysis, ensure adequate data collection and follow-up on all patients for efficacy and safety, and describe the plan for independent review of confirmed ORR in solid tumors for each substudy. If preliminary results from a substudy or substudies suggest a major advance over available therapy, the sponsor should meet with the review division to discuss modifications to the protocol.

B. Randomized Designs

If a sponsor incorporates randomization into an umbrella trial design, FDA strongly recommends use of a common control arm when possible.

C. Master Protocols Employing Adaptive/Bayesian Design

In master protocols that incorporate adaptive designs, the SAP should provide all information described in the guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*

[18] See the draft guidance for industry, FDA staff, sponsors, and IRBs *Investigational IVDs Used in Clinical Investigations of Therapeutic Products.* When final, this guidance will represent FDA's current thinking on this topic.

[19] See the draft guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination*. When final, this guidance will represent the FDA's current thinking on this topic.

[20] Simon R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, Control Clin Trials, 10(1):1–10.

and the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*[21] and describe plans for futility analyses.[22] Master protocols can use a Bayesian statistical method or other methods for planning or modifying the sample size, dropping an arm, or other adaptive strategies. The SAP should include details on implementation of Bayesian or other methods.

D. Master Protocols With Biomarker-Defined Subgroups

In master protocols with basket or complex design, where patient assignment to a treatment arm is based on the presence of a specific biomarker of interest, the protocol should clearly specify how patients with more than one biomarker of interest will be assigned to substudies. There are two approaches to making such assignments that FDA considers acceptable from a clinical trial design perspective, but other approaches may also be appropriate. One approach is to prioritize biomarkers or treatments. For example, in the BATTLE-1 trial,[23] investigators ranked the biomarker groups based on their predictive values and assigned patients with multiple biomarkers to the group for one of their biomarkers that has the highest predictive value. The other approach is based on a prespecified randomization ratio. For example, the Lung-MAP trial[10] uses a reversed ratio of prevalence rates. Using reverse prevalence ratios, patients in the trial with tumors that have biomarkers with low prevalence have a greater likelihood to be assigned to a substudy for the lower prevalence population.[24]

VIII. SAFETY CONSIDERATIONS

A. Safety Monitoring and Reporting Plans

The sponsor is required to ensure proper monitoring of the investigations and to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND.[25]

The sponsor should establish a systematic approach that ensures rapid communication of serious safety issues to clinical investigators and regulatory authorities under IND safety reporting

[21] When final, this guidance will represent the FDA's current thinking on this topic.

[22] See also the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* and the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

[23] Kim ES et al., 2011, The BATTLE Trial: Personalizing Therapy for Lung Cancer, Cancer Discov, 1(1): 44–53.

[24] See the draft guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease*. When final, this guidance will represent FDA's current thinking on this topic.

[25] 21 CFR 312.50. See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring.*

regulations.[26] In addition, the approach should describe the process for rapid implementation of protocol amendments to address serious safety issues.[27]

The original IND (see section IX., Additional Regulatory Considerations) should contain a proposed plan for periodic submissions of a cumulative summary of safety, as described under 21 CFR 312.32(c)(3), which is more frequent than annually.[28] The summary of safety should include information on any action taken for safety reasons for each investigational drug during that reporting period across the clinical development program for the investigational drug. The sponsor should reference the most recent cumulative safety report in support of protocol amendments proposing modification of existing or new substudies.

Given the complexity of and the generally rapid accrual to these trials, resulting in increased risks to patients of failure to promptly identify adverse events, sponsors should select medical monitors who have training and experience in cancer research and in the conduct of clinical trials, so that safety information can be promptly assessed.

B. Independent Safety Assessment Committee

For all master protocols, the sponsor should institute an ISAC or an IDMC structured to assess safety in addition to efficacy. 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.[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:

- Discontinuing or modifying a substudy based on safety information obtained from the protocol or from information external to the trial

- Changing the eligibility criteria if the risks of the intervention appear to be higher in a particular subgroup

- Altering the drug dosage and/or schedule if the adverse events observed appear likely to be mitigated by such changes

- Instituting screening procedures that could identify those subjects at increased risk of a particular adverse event

[26] 21 CFR 312.32.

[27] 21 CFR 312.30(b)(1) and 312.30(b)(2)(ii).

[28] 21 CFR 312.32.

[29] 21 CFR 312.32.

- Identifying information needed to inform current and future trial subjects of newly identified risks via changes in the informed consent document and, if appropriate, recommending re-consent of current subjects to continue trial participation.

C. Institutional Review Board/Independent Ethics Committee

A sponsor must not initiate a clinical trial until an IRB or independent ethics committee has reviewed and approved the protocol and the trial remains subject to continuing review by an IRB.[30] Once approved, the investigator should provide cumulative safety information to the IRB along with other information required by the IRB to allow the IRB to meet its requirements.[31]

Because of the complexity of master protocols, in general, the sponsor is expected to conduct assessment of safety more frequently than on an annual basis and to provide this information to the investigator. Sponsors are required to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use."[32] The investigator must convey this information to the IRB during the time of the IRB's continuing review, or sooner, if the information is an unanticipated problem involving risk to human subjects or others.[33] This information can include a description of the detailed plan for timely, periodic communication of trial progress; cumulative safety information; and other reports from the ISAC or IDMC. This information is necessary to allow the IRB to evaluate, for example, the risks to patients of the ongoing investigation and the adequacy of the informed consent document.

To facilitate IRB review of master protocols, FDA recommends the use of a central IRB.[34] The central IRB should have adequate resources and appropriate expertise to review master protocols in a timely and thorough manner. When necessary, an IRB can invite individuals with competence in special areas (i.e., consultants) to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB.[35]

Given the rapid accumulation of safety data and the complexity of the trial design, IRBs should consider convening additional meetings (i.e., ad hoc meetings of an existing IRB) to review the evolving safety information, provided regulatory requirements in 21 CFR part 56, such as quorum, can be met. Alternatively, a separate, duly constituted specialty IRB can be established and specifically charged with meeting on short notice to review new information and/or modifications to trials with master protocols. Such an IRB would need to satisfy the same

[30] 21 CFR 56.103(a).

[31] 21 CFR 56.109(f) and 21 CFR 312.66.

[32] 21 CFR 312.55(b).

[33] See 21 CFR 312.66 and the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs — Improving Human Subject Protection.*

[34] 21 CFR 56.114. See the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials.*

[35] 21 CFR 56.107(f).

requirements of any IRB (i.e., 21 CFR part 56); however, it could be designed to facilitate a quorum by keeping membership to a minimum (i.e., 21 CFR 56.107 requires that each IRB have at least five members) and being composed of experienced members who are capable of meeting and reviewing trial-related materials on short notice. Ad hoc meetings of an existing IRB or the establishment of a separate specialty IRB designed to facilitate the review of trials with master protocols are acceptable approaches that, if appropriately constituted and operated, can satisfy the regulatory requirement for IRB oversight.

Irrespective of the type of IRB that is used, if the master protocol includes plans to enroll pediatric patients in the trial, we recommend the IRB include (either as a member or an invited nonvoting expert) an individual or individuals who have expertise in the management of pediatric oncology patients and experience with the regulatory requirements, including parental permission and assent requirements, for the enrollment of pediatric patients in clinical investigations.[36]

D. Informed Consent Document

In addition to submitting informed consent documents to the IRB for review, the Sponsor may need to submit the original and all updated informed consent documents to the IND to allow FDA to assess that patients have the information to make informed decisions regarding participation in the trial.

In addition to new safety information, updates to the informed consent document should include all clinically important protocol modifications. Protocol amendments submitted under 21 CFR 312.30 should be accompanied by the revised informed consent documents unless immediate modifications are needed for patient safety, in which case the sponsor should submit the revised informed consent document as soon as possible.

IX. ADDITIONAL REGULATORY CONSIDERATIONS

Because of the complexity of master protocols and the need to avoid miscommunication that could compromise patient safety, sponsors should submit each master protocol as a new IND to FDA. For INDs that contain master protocols, sponsors should consider the following:

- The master protocol should be the only trial that is conducted under the IND.

- The sponsor should submit the master protocol(s) to the review division in CDER or CBER responsible for reviewing the primary indication(s). If more than one indication is being investigated, the sponsor should submit the IND to the most appropriate clinical review division within the Office of Hematology and Oncology Products in CDER, taking into account the population to be studied, or to CBER.

[36] 21 CFR 50 subpart D.

X. CONTENT OF A MASTER PROTOCOL

A. New IND Submission

Master protocols are subject to all the requirements under 21 CFR 312. To ensure that all required aspects are complete, a master protocol should contain the required elements for clinical protocols described in 21 CFR 312.23(a)(6)(iii) and all the information described in sections V, VI, VII, and VIII of this guidance. Specifically, the protocol and IND submission should address the following elements:

- Core elements as required per 21 CFR 312.20-23
- Submission in electronic (electronic common technical document (eCTD)) format
- Appropriate letters of authorization for each investigational drug
- Suggested IND title as "PROTOCOL NAME: List of investigational drugs" (e.g., LUNG-MAP: Drug X, Drug Y, Drug Z)
- Submission of each substudy within the same IND under a separate folder in Section 5.3.5. of the eCTD (as shown in Figure D in the Appendix) to facilitate review
- Inclusion of a list of all the substudies in Section 5.2 of the eCTD, in addition to the master protocol title (as shown in Figure E in the Appendix)

The master protocol should also include the following:

- A detailed description of the trial design as text and as a visual depiction
- Procedures for sample acquisition, handling, and testing of biomarkers, as appropriate
- Prominent identification of all substudies
- Description of all groups responsible for monitoring patient safety (e.g., IRB, ISAC, IDMC).
- Description of the plan for submission of interim safety and efficacy results
- The proposed informed consent document

B. Amendments to the Master Protocol

Protocol amendments that substantively affect the safety or scope of the master protocol should contain the following:[37]

- A clean and tracked changes version of the amended master protocol document
- A list of the proposed changes in tabular format with the rationale for each proposed change and the following supportive information, if available:
  - Summary of available safety and efficacy data
  - New nonclinical toxicology or pharmacology data and clinical data as appropriate to support the protocol modification
  - An updated informed consent document

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.

XI. COMMUNICATION AND INTERACTIONS WITH FDA

Sponsors should consult guidances for industry for best communication practices[38] and meetings[39] with FDA to ensure open lines of dialogue before and during the drug development process. With regard to master protocols, sponsors should consider the following:

- FDA strongly encourages a sponsor to request a pre-IND meeting. This can allow the sponsor and FDA to reach key agreements on the design and conduct of the protocol.
- The cover letter for all meeting requests should clearly state "REQUEST FOR MEETING-MASTER PROTOCOL (Meeting Type)."

[37] See 21 CFR 312.30(d) and 312.31(b) for content and format requirements for protocol amendments and information amendments.

[38] See the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development.*

[39] See the draft guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* and *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products.* When final, this guidance will represent the FDA's current thinking on this topic.

- The sponsor should notify the regulatory project manager via secure email or a phone call 48 hours before submitting any protocol amendment that substantively affects the safety or scope of the protocol.

- The cover letter for such protocol amendments should be clearly marked as "Protocol Amendment-MASTER PROTOCOL."

- If the amendment contains changes needed to eliminate an apparent immediate hazard to subjects (e.g., closure of a substudy for unacceptable toxicity, modification of eligibility or monitoring to mitigate the risks), the sponsor *should implement immediately* the revised protocol. The sponsor should ensure that FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c).[40] For other substantive changes that affect safety, scope, or the scientific quality of the study, the cover letter should contain a statement that the revised protocol will not be initiated until 30 days after submission to the IND to allow FDA to assess the risks of the proposed change and until the change has been approved by the IRB.[41]

[40] 21 CFR 312.30(b)(2)(ii).

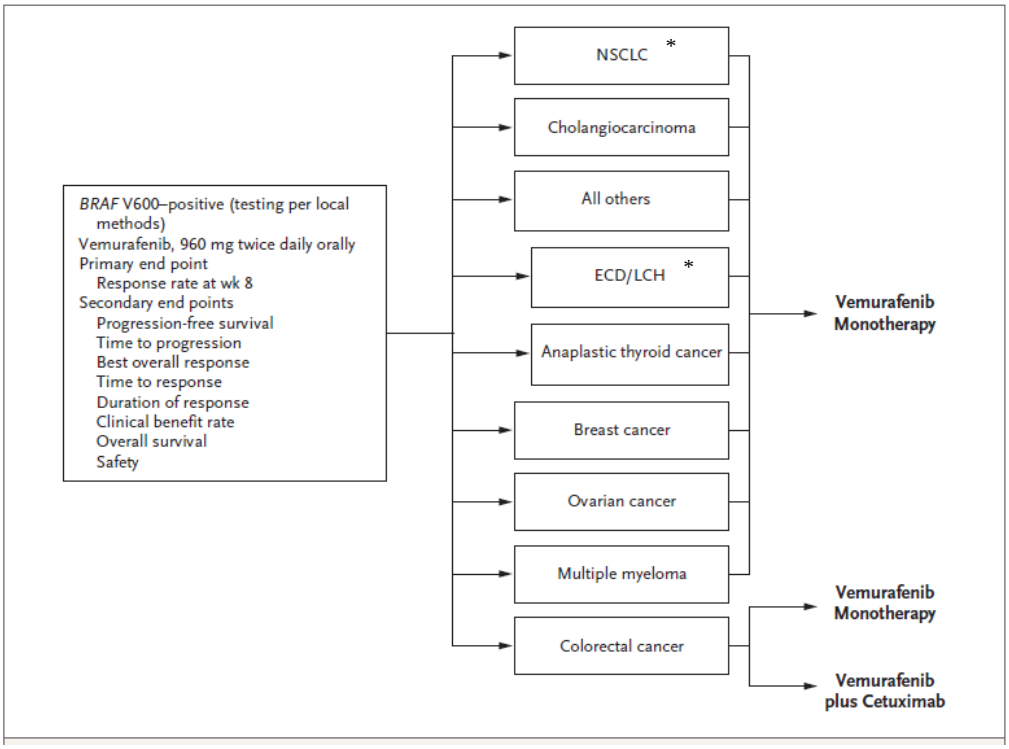
[41] 21 CFR 312.30(b)(2)(i)(b).

APPENDIX

Example of a Master Protocol With a Basket Trial Design

An example of a master protocol with basket design is the phase 2 trial evaluating vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations, as shown in Figure A.

Figure A: Vemurafenib in Nonmelanoma Cancers Harboring BRAF V600 Mutations[1]



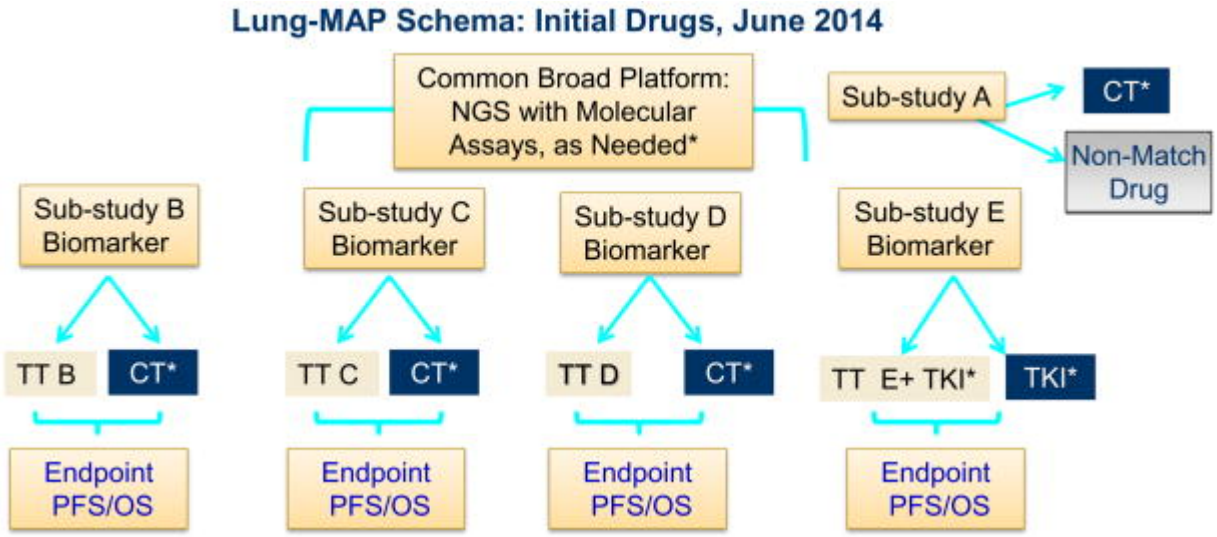
*NSCLC = Non-small cell lung cancer; ECD = Erdheim-Chester disease; LCH = Langerhans cell histiocytosis.

[1] Hyman DM et al., 2015, "Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations, N Engl J Med, 373(8):726-736.

Example of a Master Protocol With an Umbrella Trial Design

An example of a master protocol with an umbrella design is the original version of the LUNG-MAP trial, a multidrug, multi-substudy, biomarker-driven trial in patients with advanced/metastatic squamous cell carcinoma of the lung, as shown in Figure B.

Figure B: LUNG-MAP Trial in Patients With Squamous Cell Carcinoma of the Lung[2]



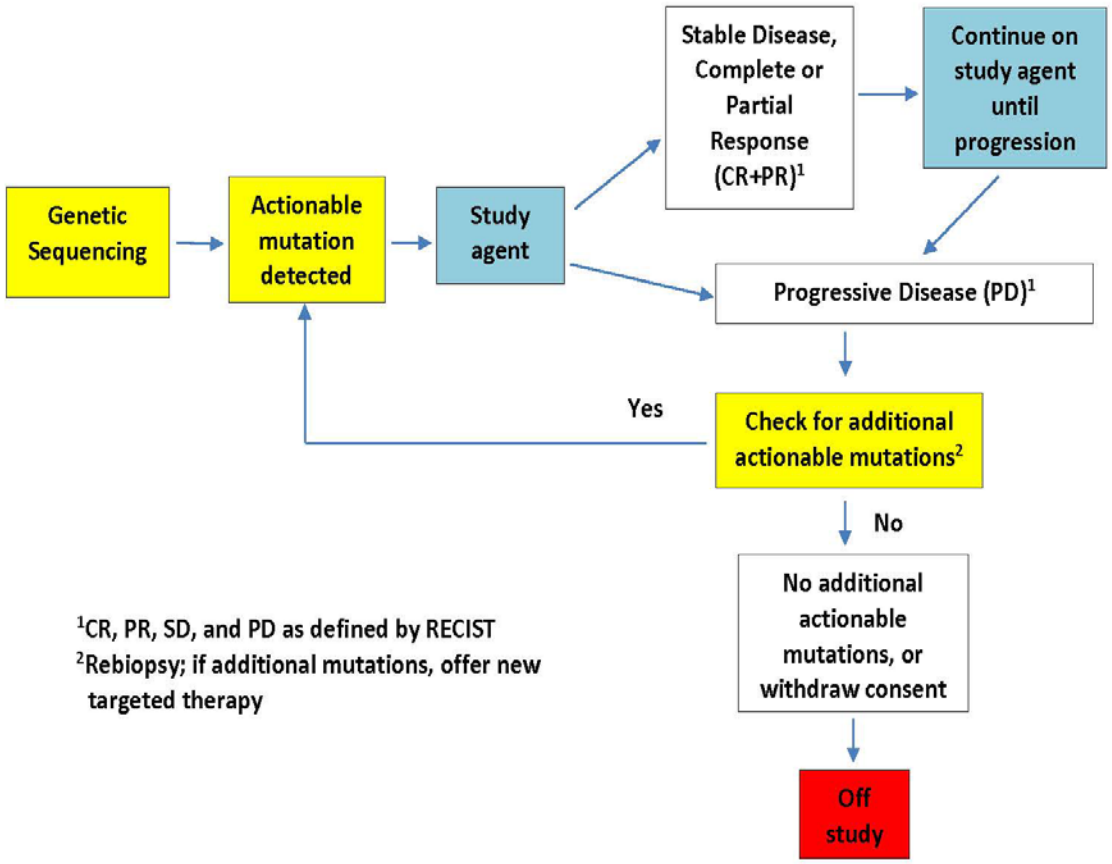
*Archival formalin-fixed, paraffin-embedded tumor, fresh core needle biopsy if needed. NGS = next generation DNA sequencing; OS = overall survival; PFS = progression free survival; TT = targeted therapy; CT = chemotherapy (docetaxel or gemcitabine); TKI = tyrosine kinase inhibitor (erlotinib).

[2] Herbst RS et al, 2015, Lung Master Protocol (Lung-MAP)- A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400, Clin Cancer Res,21(7):1514-1524.

Example of a Master Protocol With a Complex Trial Design

An example of a master protocol with a complex trial design is the NCI-MATCH trial, as shown in Figure C.

Figure C: National Cancer Institute Match Trial Scheme[3]



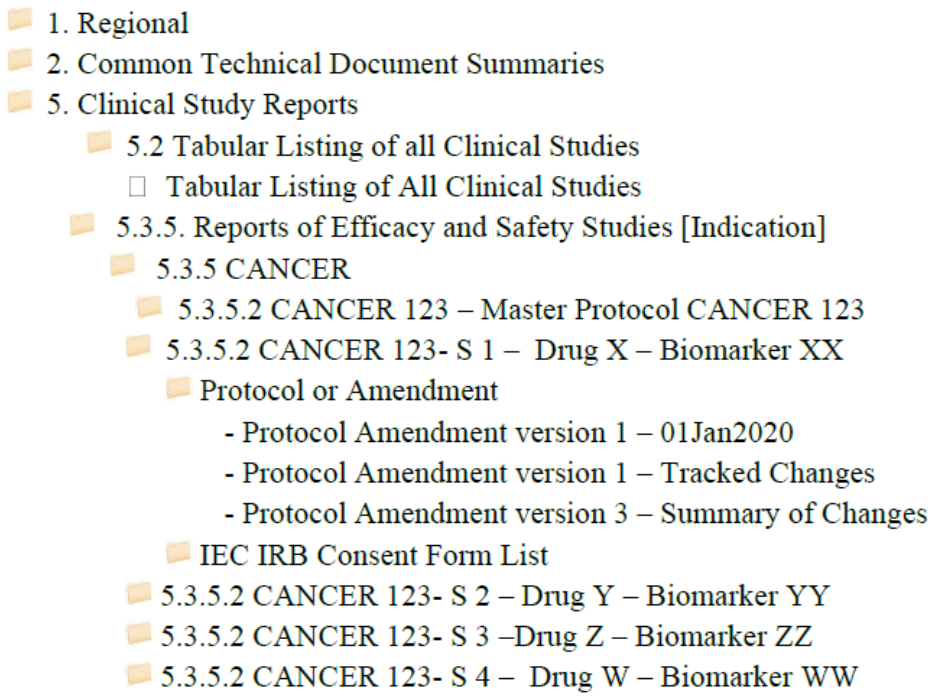
* RECIST = response evaluation criteria in solid tumors.

[3] Adapted from Abrams J et al., 2014, National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network, Am Soc Clin Oncol Educ Book: 71-6, doi: 10.14694/EdBook_AM.2014.34.71.

Examples of How to Use eCTD for a Master Protocol

Figure D (below) gives an example of how a sponsor can submit each substudy within the same investigational new drug application under a separate folder in section 5.3.5. of the electronic common technical document (eCTD).

Figure D: Schematic Figure of eCTD with an IND with Master Protocol "CANCER 123" and Substudies S-1, S-2, S-3, and S-4*



* eCTD = electronic common technical document; IND = investigational new drug application.

Figure E (below) gives an example of how a sponsor can include a list of all the substudies in section 5.2 of the eCTD, in addition to the master protocol title.

Figure E: Module 5.2 of eCTD Tabular Listing of All Clinical Studies and Substudies*

Study Identifier	Location of Study	Objectives of the Study	Study Design and type of control	Test products, Dosage regimen, Route of Administration	No. of subjects or diagnosis of patients	Healthy subjects or diagnosis of patients	Duration of Treatment	Study status; type of report
Master CANCER123								
CA123-S1								
CA123-S2								
CA123-S3								
CA123-S4								

* eCTD = electronic common technical document.