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

Guidance for Industry

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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March 2022
Procedural

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Contains Nonbinding Recommendations

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

This guidance represents 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 office 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) should have 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 recommendations 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 first-in-human or early stage clinical trials using expansion cohorts to expedite drug development. FDA addresses that topic in the draft guidance for industry

[1] This guidance has been prepared by the Office of Oncologic Diseases 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 to biological products that are regulated as drugs.

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

Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics (August 2018).[4]

There are many aspects of study design, statistical analysis, choice of study endpoints, and development of biomarkers that are not addressed in this guidance but are considered in other FDA guidances, including the guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), which were developed by the International Conference for Harmonisation (ICH) and adopted by FDA, as well as the guidance for industry *In Vitro Companion Diagnostic Devices* (August 2014).[5]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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 (i.e., trials intended to provide substantial evidence of effectiveness) 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 a variety of terms such as *umbrella*, *basket*, or *platform* describing specific designs (Woodcock and LaVange 2017). Examples of trials using master protocols include the Lung-MAP trial (NCT02154490; see Figure B in the Appendix),[6] the NCI-MATCH trial (EAY131, NCT02465060; see Figure C in the Appendix),[7] and the Pediatric MATCH trial (APEC1621, NCT03155620).[8] 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

[4] When final, this guidance will represent the 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/regulatory-information/search-fda-guidance-documents.

[5] See also the guidances for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013), *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019), and *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[6] See information on this trial at https://www.clinicaltrials.gov/.

[7] 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 as well as https://www.clinicaltrials.gov/.

[8] See information on this trial at https://www.clinicaltrials.gov/.

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, which evaluate multiple drugs and/or disease populations, and their intent to support regulatory approval, it is important that such trials be well designed and well conducted to help ensure human subject safety and to generate data that meets regulatory standards for demonstrating each investigational drug's safety and effectiveness.[9]

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 involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure. In general, FDA recommends that the sponsor establish the RP2D for the investigational drug or drugs before evaluation using a master protocol. However, individual drug substudies under the master protocol might incorporate an initial dose-finding phase, for example, in pediatric subjects when sufficient adult data are available to inform a starting dose and the investigational drug provides the prospect of direct clinical benefit to pediatric subjects (21 CFR 50.52).

A master protocol may be used to conduct the trial or trials for exploratory purposes or to support a marketing application and can be structured to evaluate, in parallel, different drugs compared with their respective controls or to a single common control. The sponsor can design the master protocol with a fixed or an adaptive design[10] 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 can also create challenges in the

[9] Under 42 U.S.C. § 282(j), including its implementing regulations in 42 CFR part 11, certain applicable clinical trials must be registered at https://www.clinicaltrials.gov/. Within 1 year of the primary completion date, with certain exceptions for submission beyond 1 year, responsible parties must submit required summary results information to https://www.clinicaltrials.gov/. FDA encourages responsible parties to submit summary results information as soon as possible and ahead of required statutory and regulatory deadlines.

[10] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics.*

conduct and analysis of the trial that, if not properly addressed, can increase risk to human subjects or delay the development of the drug.[11]

Examples of potential challenges include the following:

(1) Difficulty attributing adverse events to one or more investigational drugs can occur when multiple drugs are administered within each investigational treatment arm and the trial lacks a single internal control for those drugs.

(2) 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.

(3) The presence of multiple study groups allows potential *overinterpretation* of findings, resulting in delays in drug development. For example, an apparent difference in efficacy in a biomarker-defined subpopulation could be identified based on multiple ad hoc between-arm comparisons that prove to be false.

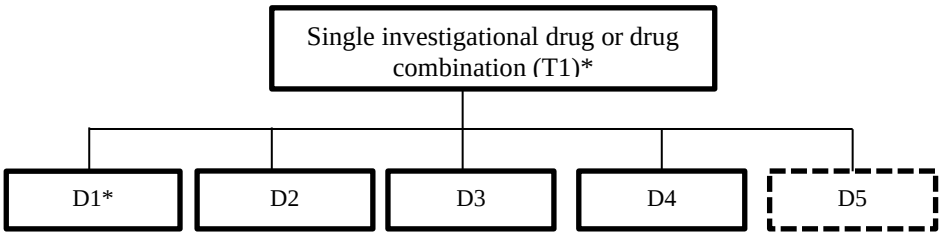
IV. TYPES OF MASTER PROTOCOLS

This section provides examples of types of master protocols and considerations related to their designs. FDA 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 of the protocol to an IND.

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 different cancers, disease stages for a specific cancer, histologies, number of prior therapies, genetic or other biomarkers, or demographic characteristics is commonly referred to as a *basket trial* (shown in Figure 1). A basket trial evaluating an investigational drug combination may include a dose-finding or safety lead-in component to identify safe doses of the combination before proceeding with an activity-estimating component.

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



[11] See also the ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

* T = investigational drug; D = protocol-defined subpopulation in multiple disease subtypes; D5 = dashed lines indicate potential amendments to include additional subpopulations.

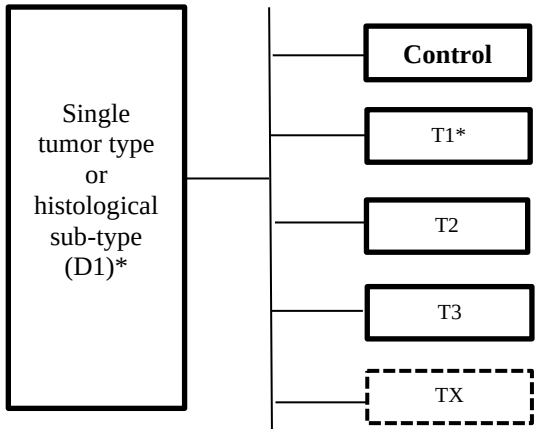
The substudies within basket trials are usually designed as single-arm, activity-estimating trials with overall response rate as the primary endpoint. A strong response signal seen in a substudy may allow for expansion of the substudy to generate data that could potentially support a marketing application. 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 or efficacy. For specific aspects related to design and analysis related to a master protocol for a basket trial, see section V., Specific Design Considerations in Master Protocols, and section 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 (see Figure A in the Appendix) (Hyman et al. 2015).

B. Investigational Drugs or Investigational Drug Combinations in Single Cancer Type

A master protocol that is designed to evaluate multiple investigational drugs administered as single drugs or as drug combinations in a single disease population is commonly referred to as an *umbrella trial* (shown in Figure 2). Substudies within umbrella trials can include dose-finding or safety lead-in components to identify safe doses of an investigational drug combination before proceeding with an activity-estimating component. As previously stated, 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 or investigational drug combination; D = protocol defined subpopulation in single disease subtypes; TX = dashed lines indicate potential amendments to include future treatment arms.

Umbrella trials can employ randomized controlled designs to compare the activity of the investigational drug or drugs 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 section V., Specific Design Considerations in Master Protocols, and section VII., Statistical Considerations.

An example of a master protocol with umbrella trial design is the original version of the LUNG-MAP trial, a multidrug, multi-substudy, biomarker-driven trial in human subjects with advanced/metastatic squamous cell carcinoma of the lung where docetaxel was the common control arm in four of the five substudies (Herbst et al. 2015). Eligible subjects were assigned to substudies based on their biomarkers or to a *nonmatch* therapy substudy for subjects not eligible for the biomarker-specific substudies. Within the substudies, subjects 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, which aims to establish whether human subjects 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) (Abrams et al. 2014).

V. SPECIFIC DESIGN CONSIDERATIONS IN MASTER PROTOCOLS

A. Use of a Single Common Control Arm

For oncology clinical trials, 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 a new drug approval or new scientific evidence, making it no longer ethical to randomize human subjects to the previous SOC. In that case, the sponsor should suspend subject enrollment until the protocol and the protocol informed consent document are modified to include the new SOC as control. The SAP should be modified as soon as possible and before any analysis of the data.

In general, comparative analyses should 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). Where an IND sponsor has right of

reference to data in more than one experimental arm, a comparison between such experimental arms might also be proposed prospectively.

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 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. 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 subjects treated at the proposed dosage for the drug combination regimen should be available before proceeding with the efficacy evaluation. The sponsor should submit results of the dose-finding phase to the IND for the master protocol before proceeding with the efficacy phase. If such an approach is considered in a pediatric population, the sponsor should ensure, for a particular tumor type and/or relevant mutations, that the full relevant age range of pediatric subjects (generally speaking 0 to ≤17 years of age) is addressed and the investigational drug provides the prospect of direct clinical benefit to pediatric subjects. For additional requirements that pertain to clinical investigations in pediatric subjects, see 21 CFR 50 subpart D. Specific age eligibility should depend on the prevalence of the particular tumor type in children.

For clinical development programs designed to evaluate combinations of two or more investigational drugs, it is important that the general investigational plan describe the approach to demonstrating the contribution of each investigational drug to the observed treatment effect to support a benefit-risk assessment.[12]

C. Studies With Drugs Targeting Multiple Biomarkers

FDA recommends early discussion with the review division of biomarker development plans when the sponsor plans to use one or more biomarkers to inform human subject selection for trials. The sponsor should provide the rationale for conducting the substudy in a biomarker-defined population, such as a tumor biomarker likely to predict a therapeutic response to the investigational drug based on the drug's purported mechanism of action (drug target) or a biomarker that enriches the study for subjects with one or more prognostic factors. For master protocols with drugs targeting multiple biomarkers, it is important that subject selection tests be analytically validated with well-defined criteria for marker positivity before initiation of the trial.

[12] See the guidances for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* and *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products.*

In master protocols containing substudies with drugs that target multiple biomarkers, the protocol should contain a prespecified plan for allocation of subjects who are potentially eligible for more than one substudy. Human subject 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 section 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.[13]

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 reestimation of the sample size based on the results of an interim analysis or discontinuation of an experimental arm based on futility rules.

E. Independent Data Monitoring Committees

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, as appropriate. In addition, the protocol should describe and provide a charter for an independent data monitoring committee (IDMC) or other appropriate independent entity to monitor efficacy and safety results.[14] 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.

Pediatric expertise should be provided on IDMCs that will review pediatric studies; an ethicist should be considered for all studies, pediatric and adult. For additional responsibilities related to safety monitoring, see section VIII. B., Independent Safety Assessment.

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, either as single biomarker tests or as a platform assessing multiple biomarkers, that are analytically validated. Use of IVDs

[13] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics.*

[14] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

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

Sponsors should establish procedures for sample acquisition, handling, and the testing and analysis plans as early as possible in the biomarker development program. Sponsors should discuss with the review division whether 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, sponsors and institutional review boards (IRBs) should assess what investigational device requirements[16] apply using the definitions in 21 CFR 812.3 and the criteria found in 21 CFR 812.2 that address the level of risk that the device presents to trial subjects (i.e., significant risk, nonsignificant risk) and address exempted device investigations.[17,18] Clinical investigations of devices that pose a significant risk generally require both FDA and IRB approval before initiation.[19] FDA approval can be obtained through submitting an investigational device exemption (IDE) application to FDA (§ 812.20).[20] 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 about 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.[21]

Sponsors 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.

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[15] See the draft guidance for industry and FDA staff, *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product* (July 2016). When final, this guidance will represent FDA's current thinking on this topic.

[16] 21 CFR part 812.

[17] See the guidance for sponsors, clinical investigators, IRBs, and FDA staff *FDA Decisions for Investigational Device Exemption Clinical Investigations* (August 2014) 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* (August 2013).

[18] See the draft guidance for industry, FDA staff, sponsors, and IRBs *Investigational IVDs Used in Clinical Investigations of Therapeutic Products* (December 2017). When final, this guidance will represent FDA's current thinking on this topic.

[19] 21 CFR 56.103 and 812.20.

[20] See the guidance for sponsors, clinical investigators, IRBs, and FDA staff, *FDA Decisions for Investigational Device Exemption Clinical Investigations*. Additional information is available at https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-approval-process.

[21] See the guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination* (October 2019).

VII. STATISTICAL CONSIDERATIONS

A. Nonrandomized, Activity-Estimating Design

In nonrandomized protocols, where the primary endpoint is overall response rate, 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, that limit exposure to an ineffective drug (Simon 1989). However, other statistical approaches may be acceptable and, if proposed, should be described in detail in the SAP. If a sponsor anticipates that the results would form the 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. 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 (e.g., to propose interim analyses for efficacy or consider early termination of the trial) or to modify the development program (e.g., discuss potential for breakthrough therapy designation).

B. Randomized Designs

If a sponsor incorporates randomization into an umbrella trial design, FDA recommends use of a common control arm when possible. The general comments about generation of an appropriate SAP and information about futility analysis in the previous section (VII. A., Nonrandomized, Activity-Estimating Design) also apply to randomized trials. Before initiating the proposed substudy, the sponsor should meet with the division to discuss the SAP with regard to how the strength of evidence will be assessed and how potential sources of bias will be controlled.

C. Master Protocols Employing Adaptive/Bayesian Design

In master protocols that incorporate adaptive designs, the SAP should provide all information described in the guidances for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* and *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products.* The SAP should also 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, and 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 human subject assignment to a treatment arm is based on the presence of a specific biomarker of interest, the protocol should clearly specify how subjects with more than one biomarker of interest will be assigned to

[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*.

substudies. There are two approaches to making such assignments that FDA recommends 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, investigators ranked the biomarker groups based on their predictive values and assigned human subjects with multiple biomarkers to the group for one of their biomarkers that has the highest predictive value (Kim et al. 2011). The other approach is based on a prespecified randomization ratio. For example, the Lung-MAP trial uses a reversed ratio of prevalence rates. Using reverse prevalence ratios, subjects 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.[23] Consideration should be given to the clinical relevance, if any, of low-prevalence passenger mutations that coexist with driver mutations, for which adjustment to randomization may not be needed. Sponsors should provide justification for the selected approach and should state in the justification whether the proposed approach of assigning subjects with more than one biomarker of interest to a particular substudy would impact the prevalence of the biomarkers in each subpopulation and whether any statistical methods to address this potential issue/bias are needed.

VIII. SAFETY CONSIDERATIONS

A. Safety Monitoring and Reporting Plans

The sponsor of the master protocol IND 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 (21 CFR 312.50).[24] Similarly, the sponsor of the investigational product IND for a drug that will be administered under a master protocol IND is responsible for monitoring the safety of its drug and evaluating all accumulating safety data, including data from trials not conducted by the sponsor of the investigational product IND (21 CFR 312.32(b)). The sponsor of the master protocol IND should establish a systematic approach that ensures rapid communication of serious safety issues to all participating clinical investigators and FDA under IND safety reporting regulations.[25] Additionally the master protocol IND sponsor should ensure rapid communication of serious safety issues to the sponsors of all products used in the master protocol, according to the established safety reporting plan. In addition, the approach should describe the process for rapid implementation of protocol amendments to address serious safety issues.[26]

Safety monitoring and reporting obligations of the sponsor of the master protocol IND and sponsors of each IND covered by the master protocol remain unchanged in master protocol trials.

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[23] See the guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease* (October 2018).

[24] See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013).

[25] 21 CFR 312.32.

[26] 21 CFR 312.30(b)(1) and 312.30(b)(2)(ii).

These reporting obligations are described, along with recommendations to help sponsors comply with expedited safety reporting requirements, in the draft guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021).[27]

For master protocols in oncology, FDA may expect a sponsor to conduct aggregate analyses of all SAEs at intervals based on the volume of safety data collected or based on the number of subjects accrued into the master protocol in order to fulfill its review obligations under 312.32(b). A sponsor would then be required to submit events that qualify for reporting under 312.32(c) and as described in the draft guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies*. The frequency of the cumulative aggregate safety analyses should be discussed with the Agency at a pre-IND meeting, taking into account specific program needs.

Given the complexity of and the generally rapid accrual to these trials, resulting in increased risks to subjects should there be a failure to promptly identify suspected and unexpected serious adverse reactions, 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

For all master protocols, the sponsor should institute an IDMC or other appropriate independent entity structured to assess safety in addition to efficacy (section V. E., Independent Data Monitoring Committee). 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.[28] The IDMC or other appropriate independent entity 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:

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

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

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

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

[28] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* and the draft guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies*.

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

(5) 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 reconsent of current subjects to continue trial participation

For more information regarding entities that review aggregate data for IND safety reporting, see section VI of the guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies*.

C. Institutional Review Board/Independent Ethics Committee

A clinical trial being conducted under a master protocol IND must not be initiated until an IRB or independent ethics committee has reviewed and approved the protocol, and the trial remains subject to continuing review by an IRB.[29] After initiation, modifications to the master protocol must be approved by the IRB or independent ethics committee before implementation, with the exception of protocol amendments that are necessary to eliminate apparent immediate hazards to trial participants, which can generally be immediately implemented but are required to be reported to the IRB afterward.[30]

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."[31] Investigators are required under § 312.66 to report all "unanticipated problems involving risk to human subjects or others" to the IRB. FDA considers a serious and unexpected adverse event that meets the criteria for sponsor reporting to FDA and all investigators in an IND safety report under § 312.32 to be an "unanticipated problem[ ] involving risk to human subjects or others" that therefore must be reported to the IRB by the investigator. 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.[32] 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 IDMC. This information is necessary to allow the IRB to evaluate, for example, the risks to human subjects of the ongoing investigation and the adequacy of the informed consent document.[33]

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[29] 21 CFR 56.103(a); 21 CFR 312.66.

[30] 21 CFR 56.108(a)(4), 56.104(c), and 21 CFR 312.66.

[31] 21 CFR 312.55(b).

[32] See 21 CFR 312.66 and the draft guidance for industry *Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices* (September 2021).When final, this guidance will represent the FDA's current thinking on this topic.

[33] 21 CFR 56.109(f).

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. In its discretion, an IRB can invite individuals with competence in special areas (i.e., consultants) to help review complex issues that require expertise beyond or in addition to that available on the IRB.[35]

For research conducted under a master protocol, safety data may rapidly accumulate. IRBs should consider convening additional meetings (i.e., ad hoc meetings of an existing IRB) to review the safety data that the investigator has provided to the IRB for any unanticipated problem involving risk to human subjects or others. The purpose of such meetings would be to expeditiously review the unanticipated problems and, if needed, any proposed trial modifications. Alternatively, a separate, duly constituted specialty IRB can be established and specifically charged with meeting on short notice to review new information and modifications to trials with master protocols. Such an IRB would need to satisfy the same 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 subjects in the trial, FDA recommends 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.[36] IRBs reviewing protocols involving pediatric subjects also should include an individual or individuals with experience with the regulatory requirements for the inclusion of pediatric subjects in clinical trials, including the requirements for parental permission and assent.[37]

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 human subjects have the information to make informed decisions about participation in the trial (21 CFR 50.20). Depending upon the design of the trial, a sponsor may consider the use of informed consent documents specific to each substudy.

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[34] See 21 CFR 56.114 and the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials* (March 2006).

[35] 21 CFR 56.107(f). These individuals may not vote with the IRB.

[36] 21 CFR 56.107.

[37] 21 CFR 56.107 and 21 CFR 50 subpart D.

In addition to new safety information, updates to the informed consent document to reflect protocol modifications may be required.[38] Protocol amendments submitted under 21 CFR 312.30 should be accompanied by the revised informed consent documents unless immediate modifications are intended to eliminate an apparent immediate hazard to subjects, 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 subject safety, sponsors should submit each master protocol as part of 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 to the review division in CDER or CBER responsible for reviewing the primary indication or indications. 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 Oncologic Diseases in CDER, or within CBER, taking into account the population to be studied.

X. CONTENT OF A MASTER PROTOCOL

A. New IND Submission

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

(1) Core elements as required per 21 CFR 312.20-23

(2) Submission in electronic (electronic common technical document (eCTD)) format[39]

The protocol and IND submission should also address the following elements:

(3) Appropriate letters of authorization to the other INDs for each investigational drug also being studied under the IND for the master protocol indicating the location of chemistry,

[38] 21 CFR 50.25(a).

[39] See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance* (February 2020).

manufacturing, and controls; nonclinical pharmacology and toxicology; clinical pharmacology; and clinical information in the IND referenced in support of the master protocol IND

(4) Suggested IND title as "PROTOCOL NAME: List of investigational drugs" (e.g., LUNG-MAP: Drug X, Drug Y, Drug Z)

(5) 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

(6) 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:

(1) A detailed description of the trial design as text and as a visual depiction

(2) Procedures for sample acquisition, handling, and testing of biomarkers, as well as information pertaining to any IVDs employed in the trial, as appropriate

(3) Prominent identification of all substudies

(4) Description of all groups responsible for monitoring subject safety (e.g., IRB, IDMC)

(5) Description of the plan for submission of interim safety and efficacy results

(6) 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:[40]

(1) An updated informed consent document

(2) A clean and tracked changes version of the amended master protocol document

(3) A list of the proposed changes in tabular format with the rationale for each proposed change and the following supportive information, if available:

(a) Summary of available safety and efficacy data

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

(b) New nonclinical toxicology or pharmacology data and clinical data as appropriate to support the protocol modification

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 master protocol 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 master protocol 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[41] and meetings[42] 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 encourages the sponsor of the master protocol 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)."

- 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 intended 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.[43] The sponsor must ensure that FDA is subsequently notified by protocol

[41] See the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017).

[42] See the draft guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018) and *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, these guidances will represent the FDA's current thinking on these topics.

[43] See 21 CFR 312.30(b)(2)(ii) (allowing protocol changes intended for this purpose to be "implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).").

amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c).[44] 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.[45]

[44] See 21 CFR 56.104(c) (permitting IRB exemption for emergency use of a test article).

[45] See 21 CFR 312.30(b)(2)(i)(b) (permitting a protocol change to be made once the sponsor has submitted the change to FDA and the change has been approved by the IRB).

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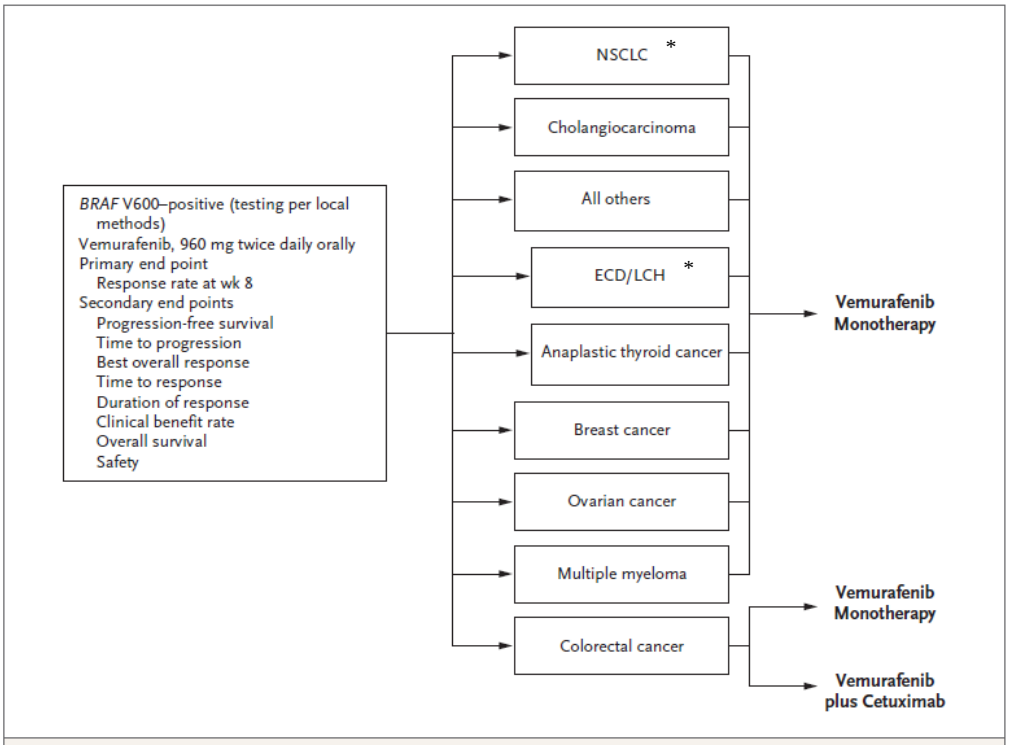
APPENDIX

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]



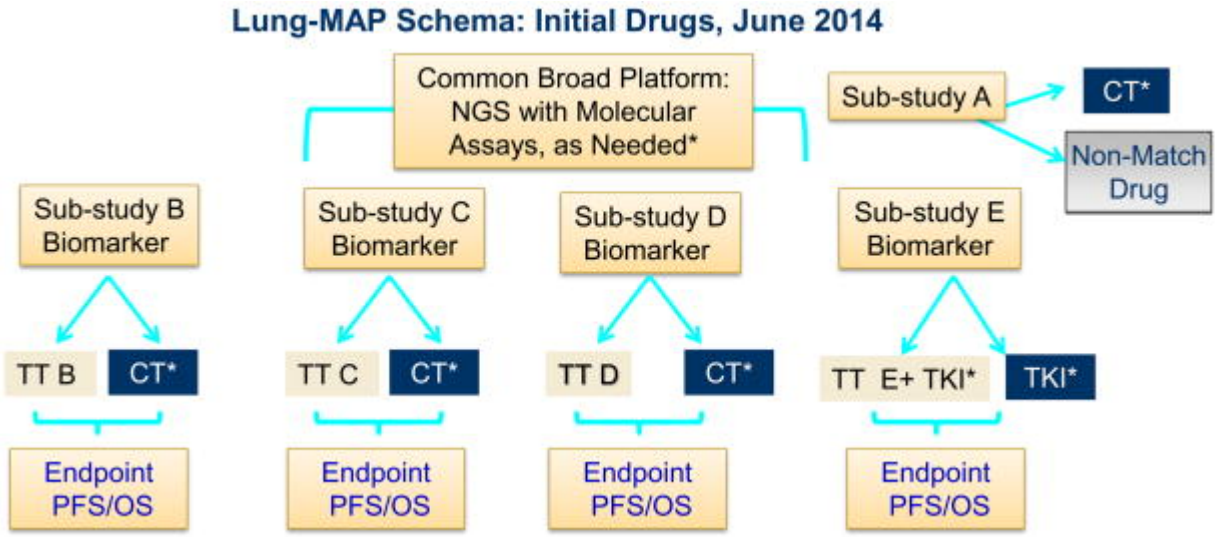
*NSCLC = Non-small cell lung cancer; ECD = Erdheim-Chester disease; LCH = Langerhans cell histiocytosis.

[1] Hyman DM, I Puzanov, V Subbiah, JE Faris, I Chau, J-Y Blay, J Wolf, NS Raje, EL Diamond, A Hollebecque, R Gervais, ME Elez-Fernandez, A Italiano, R-D Hofheinz, M Hildago, E Chan, M Schuler, SF Lasserre, M Makrutzki, F Sirzen, ML Veronese, J Tabernero, and J Baselga, 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]



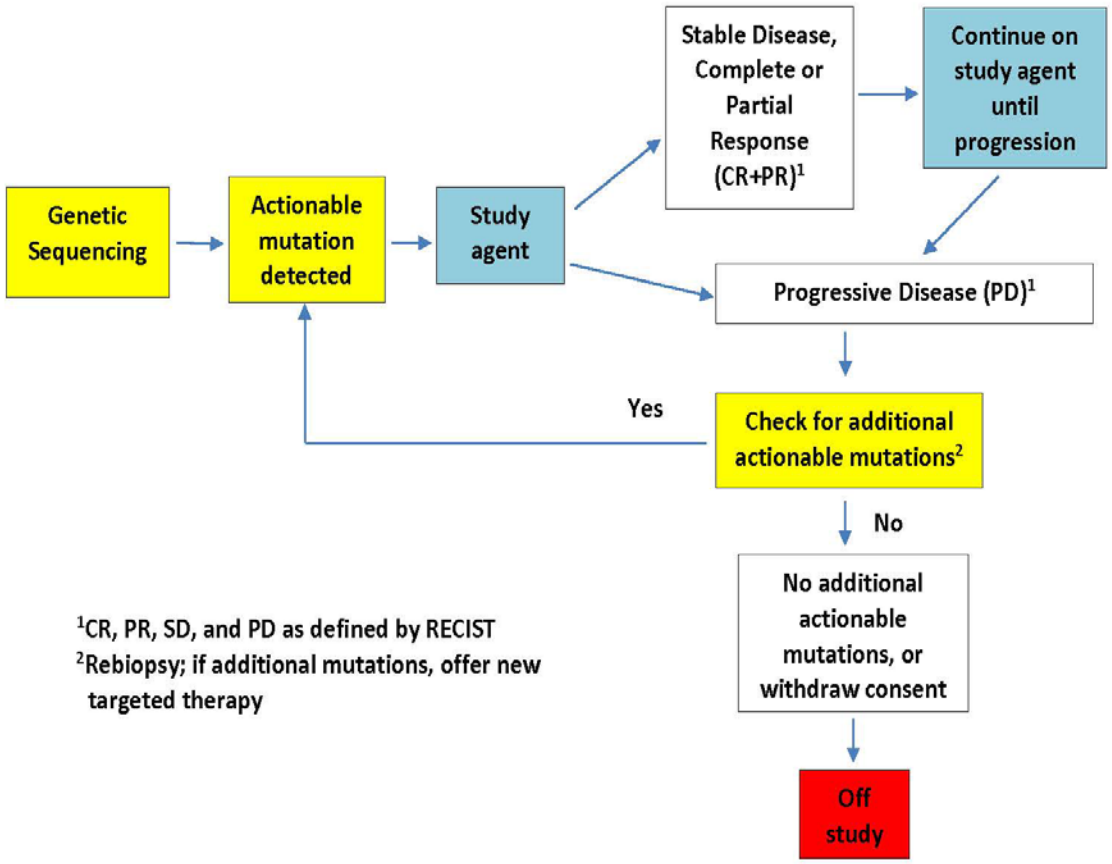
*Archival formalin-fixed, paraffin-embedded tumor, fresh core needle biopsy if needed. NGS = next generation DNA sequencing; OS = overall survival; PFS = progression free survival; TT = targeted therapy; CT = chemotherapy (docetaxel or gemcitabine); TKI = tyrosine kinase inhibitor (erlotinib).

[2] Herbst RS, DR Gandara, FR Hirsch, MW Redman, M LeBlanc, PC Mack, LH Schwartz, E Vokes, SS Ramalingam, JD Bradley, D Sparks, Y Zhou, C Miwa, VA Miller, R Yelensky, Y Li, JD Allen, EV Sigal, D Wholley, CC Sigman, GM Blumenthal, S Malik, GJ Kelloff, JS Abrams, CD Blanke, and VA Papadimitrakopoulou, 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]



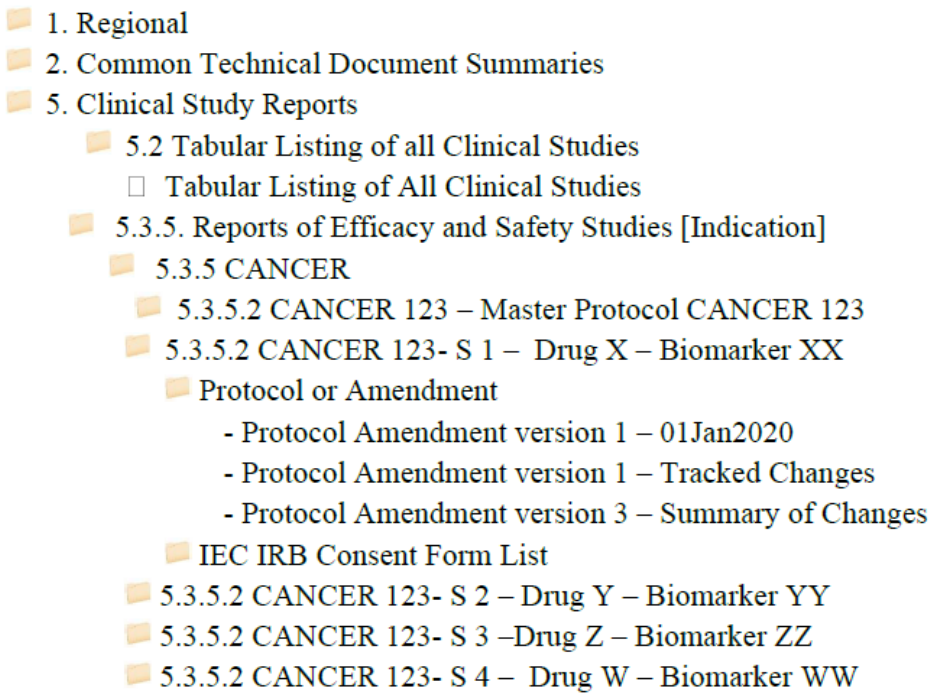
*RECIST = response evaluation criteria in solid tumors; SD = stable disease.

[3] Adapted from Abrams J, B Conley, M Mooney, J Zwiebel, A Chen, JJ Welch, N Takebe, S Malik, L McShane, E Korn, M Williams, L Staudt, and J Doroshow, 2014, National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network, Am Soc Clin Oncol Educ Book, 34:71–76.

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.