Master Protocols for Drug and Biological Product Development

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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Biostatistics / Clinical / Medical

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Master Protocols for Drug and Biological Product Development 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 document provides recommendations on the design and analysis of trials conducted under a master protocol as well as guidance on the submission of documentation to support regulatory review.[2]

For the purpose of this guidance, FDA defines the following terms:

- *Master protocol:* a protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more medical products in one or more diseases or conditions within the overall study structure.

- *Substudy*: the information and design features (e.g., objectives, design, methodology, statistical considerations) related to evaluation of a single medical product in a single disease, condition, or disease subtype in the master protocol.

Examples of trial types that could utilize a master protocol include the following:

- *Umbrella trial*: a trial designed to evaluate multiple medical products concurrently for a single disease or condition.

- *Platform trial*: a trial designed to evaluate multiple medical products for a disease or condition in an ongoing manner, with medical products entering or leaving the platform.

[1] This guidance has been prepared by the Office of Biostatistics and the Office of New Drugs in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] FDA is issuing this guidance to satisfy, in part, a mandate under section 3607(b)(2)(C-F) of the Food and Drug Omnibus Reform Act of 2022 (FDORA). Consistent with the FDORA mandate, this guidance discusses recommendations for clinical trials to streamline logistics and facilitate the efficient collection and analysis of data, as well as important principles for the evaluation of effectiveness, recommendations for communication between sponsors and the FDA, and considerations related to ensuring participant safety and data integrity in such trials.

- *Basket trial*: a trial designed to evaluate a medical product for multiple diseases, conditions, or disease subtypes.

For the purpose of this guidance, the term *master protocol sponsor* refers to the person or organization who takes responsibility for and initiates the master protocol.[3] In many instances individual drugs chosen for evaluation in the master protocol will also be evaluated under separate Investigational New Drug Applications (INDs) independent of the master protocol. A sponsor responsible for the investigation of an individual drug evaluated under the separate IND is referred to as the *individual drug sponsor*. The master protocol sponsor and the individual drug sponsor may or may not be the same entity. This guidance uses the term *sponsor* when providing general recommendations that may be relevant to both the master protocol sponsor and individual drug sponsors.

The primary focus of this guidance is on randomized umbrella and platform trials that are intended to contribute to a demonstration of safety and substantial evidence of effectiveness of a drug.[4] The concepts discussed may also be useful to consider for early-phase or exploratory umbrella and platform trials as well as those conducted to satisfy post-marketing commitments or requirements. The recommendations and considerations in this guidance do not apply to master protocols evaluating first-in-human drugs given the unique attributes from both a trial design and regulatory perspective that must be considered.[5]

The considerations in this guidance apply to a range of therapeutic areas.[6] Sponsors considering master protocols in oncology should also consult *Master Protocols: Efficient Clinical Trial Design Strategies To Expedite Development of Oncology Drugs and Biologics* (March 2022).[7] Sponsors evaluating cellular and gene therapy products in early-phase development should consult the guidance for industry *Studying Multiple Versions of Cellular or Gene Therapy Product in Early-Phase Clinical Trials* (November 2022).

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

[3] See 21 CFR 312.3.

[4] For the purposes of this guidance, all references to drugs include both human drugs and biological products unless otherwise specified.

[5] This guidance does not address first-in-human expansion cohort studies in oncology as these master protocols evaluate drugs in a limited population with serious oncologic disease for which no satisfactory alternative therapies are available. For more information on this topic, see the guidance for industry *Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics* (March 2022).

[6] In May 2021, FDA published the guidance for industry *COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention*, which focused on master protocols evaluating drugs for the treatment or prevention of COVID-19. That guidance was intended to remain in effect only for the duration of the public health emergency related to Coronavirus Disease 2019 declared by the Secretary of Health and Human Services under section 319 of the Public Health Service Act (section 319 public health emergency), which has now expired. FDA is issuing this draft guidance because many of the recommendations set forth in the 2021 guidance are applicable outside the context of the section 319 public health emergency and are applicable to other therapeutic areas, not just COVID-19.

[7] We update guidances periodically. 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.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Well-designed and -conducted trials using master protocols can accelerate drug development by maximizing the amount of information obtained from the research effort. Compared with stand-alone trials under separate protocols, a master protocol may offer certain advantages by leveraging a shared control arm and other shared protocol elements (e.g., visit schedule, measurement procedures), shared infrastructure (e.g., recruitment efforts, network of clinical sites, central facilities, central randomization system, data management systems), and shared oversight (e.g., steering committee, data review committee). Such advantages may make master protocols particularly suitable in certain settings. For example, a master protocol may be useful in settings where subject recruitment is challenging, as comparing multiple drugs to a shared placebo arm can reduce the number of subjects on placebo relative to multiple trials comparing each drug to a placebo.

At the same time, master protocols add elements of complexity, which can increase start-up time and can lead to design challenges such as ensuring adequate blinding to treatment assignment (see section III.D). Additionally, master protocols involving multiple stakeholders will require a high degree of coordination. Sponsors should carefully weigh these considerations when deciding whether a master protocol is appropriate as part of a drug development program.

A master protocol can be used to generate different types of data including proof-of-concept, dose-ranging, effectiveness, and safety data. Sponsors should consider the role of the master protocol in the overall drug development program, as this will inform its objectives and design. For example, the choice of endpoint in a master protocol may differ depending on whether the objective is to screen multiple products rapidly to determine which ones to carry forward into later stage trials versus to contribute to a demonstration of substantial evidence of effectiveness. As with other types of trials, whether the data generated by a trial conducted under a master protocol will be adequate to contribute to a demonstration of substantial evidence of effectiveness will depend on the design and conduct of the trial and the persuasiveness of its results.[8] A development program that includes a master protocol will often also include stand-alone trials given the different types of data needed to support drug development.

III. CONSIDERATIONS ON DESIGN AND ANALYSIS

This section discusses important considerations for the design and analysis of master protocols, with a focus on randomized umbrella and platform trials that are intended to contribute to a demonstration of safety and substantial evidence of effectiveness.

[8] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

A. Randomization

FDA recommends randomization of subjects to receive one of the drugs being evaluated or a control to remove systematic imbalances between treatment arms in both measured and unmeasured prognostic factors and to ensure reliable inference on the safety and effectiveness of the drugs. Sponsors should consider using a randomization scheme that allocates more subjects to the control arm than each individual drug arm, as this can increase power for each drug versus control comparison for a given total sample size (Chandereng et al. 2020 and Appendix: section A). Note that although the randomization ratio that optimizes power involves greater-than-equal allocation to the control arm, the probability that an individual subject entering the trial will be assigned to control is less than in a typical two-arm controlled trial with 1:1 randomization. This disproportionate randomization also reduces the risk of a poorly or highly performing control arm leading to multiple correlated erroneous findings (see section III.F).

It is possible for the randomization ratio to change in the setting of a master protocol. This can occur when products enter or exit a platform trial over time with certain fixed randomization schemes (i.e., schemes where the randomization ratio does not depend on accumulating covariate or outcome data from the platform trial). For example, one randomization scheme (see Appendix: section A) could change the randomization ratio from $\sqrt{2}:1:1$ (control:drug A:drug B) to $\sqrt{3}:1:1:1$ (control:drug A:drug B:drug C) when a third drug, drug C, enters a trial that had been previously evaluating two drugs, drug A and drug B. If the randomization ratio for a drug relative to the control changes, the comparisons between the drug and control should account for time periods of different randomization ratios. Possible approaches are stratifying by the time period or inverse weighting by probabilities of treatment assignments.

In settings where it is reasonable for a subject to be treated simultaneously with more than one of the multiple drugs being evaluated under a master protocol, a factorial design could also be considered. For example, subjects at trial entry could be randomized to drug A or a placebo for drug A and also randomized to drug B or a placebo for drug B, such that some subjects are assigned to receive drug A and drug B in combination. This design provides data on drugs used in combination but would not be appropriate in many circumstances, such as when drugs A and B are hypothesized to be duplicative, antagonistic, or unsafe when used together.

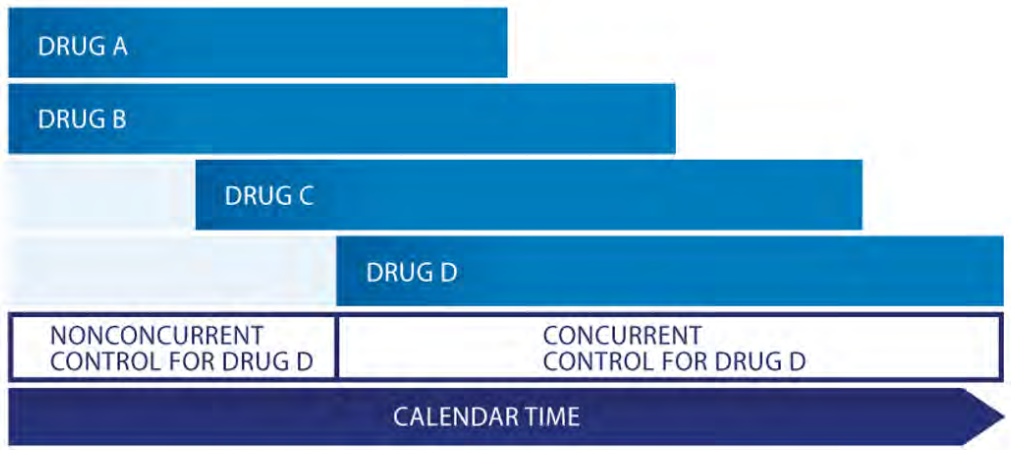
It may be necessary for master protocols to utilize drug-specific eligibility criteria in some settings (e.g., with exclusion of subjects with diminished kidney function for a drug with kidney toxicity). In these situations, protocols and randomization processes should be designed to prevent subjects from being randomized to drugs they are not eligible to receive, as this would compromise subject safety and the integrity of the randomized comparison (see additional discussion in section III.B).

B. Control Group

The choice of control group is a critical design element of any trial, including one conducted under a master protocol.[9] This guidance focuses on master protocols that include randomization to an internal control group in their design, as opposed to use of an external control. While some of the considerations discussed in this guidance on the use of nonconcurrent control data may also be relevant for the use of external control data, specific considerations for external controls in a master protocol are outside the scope of this document.[10]

One important consideration in platform trials is the composition of the control group for a given drug. A platform trial allows products to enter and exit in an ongoing manner, such that the control arm spanning the duration of the trial includes both subjects randomized to the control who were concurrently enrolled and could have been randomized to a given drug, as well as subjects nonconcurrently randomized to the control who could not have been randomized to the given drug. For example, consider a platform trial that initially randomizes subjects to one of two drugs (drugs A and B) or a shared control. At later calendar times, two additional drugs, drug C and then drug D, enter the platform. The schematic in Figure 1 illustrates such a hypothetical platform trial and depicts concurrent and nonconcurrent controls for the evaluation of drug D.

Figure 1: A Schematic to Illustrate Concurrent and Nonconcurrent Control Arm Data for Evaluating Drug D in a Hypothetical Platform Trial



The control group used for the primary comparison of any given drug in a master protocol should generally include only concurrently randomized subjects (i.e., a concurrent control) and should not include nonconcurrently randomized subjects. Use of a concurrent control preserves the integrity of randomized comparisons and ensures valid inference on the effects of the drug by

[9] The control could be placebo or active and could be used for superiority and/or non-inferiority comparisons. General considerations about the choice of control, such as those discussed in the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), are outside the scope of this document.

[10] For additional considerations on the use of external controls, see the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). When final, this guidance will represent the FDA's current thinking on this topic.

avoiding systematic differences between groups with respect to both known and unknown factors that are prognostic of the key outcomes. Systematic differences between a drug and nonconcurrent control could be caused by temporal shifts in subject characteristics,[11] trial conduct, or standard of care, especially for a long-running platform trial or in a rapidly changing clinical setting. In the presence of such temporal shifts, use of nonconcurrent control data can lead to bias in treatment effect estimates and alter the type I and type II error probabilities even if attempts are made to account for potential trends in the analysis (e.g., Lee and Wason 2020 and Jiao et al. 2019). Notably, the use of a shared control arm in platform trials leads to considerable efficiency gains relative to stand-alone trials even if comparisons for a given drug utilize only concurrent control data.

In addition to including only concurrent control data, it also important to ensure that the primary analysis for a given drug utilizes only those control arm subjects who underwent randomization that could have assigned them to that drug. For example, consider the scenario where the master protocol has some drug-specific eligibility criteria. The control arm used in the comparison for a drug should include only those subjects who met the drug eligibility criteria and could have been randomized to the given drug but were instead concurrently randomized to the control arm. Subjects who were not eligible to receive the drug and were concurrently randomized to the control should not be included in the analysis.

While use of a concurrent control group is the preferred approach to support the most robust conclusions, there may be rare circumstances in which sponsors can justify use of nonconcurrent control data. Use of nonconcurrent control data can increase the precision of inference on the treatment effect due to the increased number of subjects in the control arm. This may be particularly relevant in settings where there are different bias-variance tradeoffs, such as early-phase exploratory trials and trials in rare diseases with feasibility constraints, as long as the approach can be scientifically justified. Sponsors considering the use of nonconcurrent control data in a platform trial intended to contribute to substantial evidence of effectiveness should discuss their rationale for such an approach with the Agency early on in their planning. Information relevant to this discussion include: the feasibility of relying on only concurrent control data, the likelihood of temporal changes that could affect the treatment comparison; the amount of nonconcurrent control data to be utilized; the expected separation in calendar time between randomization of nonconcurrent control subjects and initiation of randomization to the drug of interest; and statistical methods intended to account for potential temporal changes and their underlying assumptions.

In those circumstances where use of nonconcurrent control data may be justified, sponsors should incorporate methods to address potential bias. The decision to use nonconcurrent control data should be made and agreed upon with FDA prior to the start of the trial as this will avoid a scenario where a sponsor proposes to utilize nonconcurrent data after seeing desirable results (e.g., a poorly performing control arm). Additionally, the master protocol should ensure uniform approaches to trial design and conduct, especially for characteristics likely to affect the outcome of interest and should specify the collection of known baseline prognostic variables and post-

[11] There are many reasons why characteristics of subjects entering a trial may change over time. For example, subjects entering a trial at the beginning may be more likely to have existing disease and a worse prognosis than subjects entering the trial later who may be more likely to have newly diagnosed disease.

baseline influences on the outcome (e.g., concomitant medications).[12] The planned primary analysis should incorporate approaches to mitigate potential for confounding due to changes in prognostic factors over time. For example, options may include adjustment for a function of calendar time and baseline prognostic factors, a dynamic approach for the amount of nonconcurrent control data borrowing (e.g., with a Bayesian hierarchical model), and/or a network meta-analysis to combine comparisons between concurrently randomized treatment arms. The underlying assumptions of the analysis should be described, and the operating characteristics of the analysis should be evaluated in different settings (e.g., in the presence of temporal shifts). Additionally, sensitivity analyses should be planned and conducted to understand the effect of the use of nonconcurrent control data on the evaluation of the treatment effect. For example, these may include an evaluation of the treatment effect based on only concurrent control data and/or based on increased weighting of the concurrent control data (and decreased weighting of the nonconcurrent control data) relative to the primary analysis.

Another situation that sponsors should carefully consider is when it may be appropriate to incorporate a drug evaluated under the master protocol into the trial either as part of the control arm or as background therapy. Such a change is complex because it may affect various design and analysis considerations such as whether the primary comparison for other drugs is to evaluate superiority or noninferiority, sample size calculations, and considerations around integrating data before and after the change for drugs with ongoing evaluation at the time of the change. Therefore, sponsors should seek concurrence from the Agency before implementing any such changes to the control arm or background therapy.

C. Informed Consent

The informed consent process should cover all treatment arms in the trial to which the subject could be randomized.[13,14] In a platform trial allowing drugs to enter and leave the trial over time, the consent form should be modified over time to reflect the drugs currently under evaluation.

The informed consent process should occur prior to a subject's randomization and avoid substudy-specific consent. Consent that occurs after subjects have been randomized to one of the substudies may result in subjects with different prognostic characteristics across substudies, raising concern about the comparability of each drug group with the shared control group (comprised of control subjects from different substudies). To illustrate the concern, consider a master protocol with two drugs (drug A and drug B) in which the subject consents to screening and randomization to a substudy as part of the master protocol, with a substudy-specific informed consent process to occur after randomization to that substudy; after the substudy-specific consent, the subject is then randomized to the drug or its matched control. With this process, comparing drug A against the shared control arm (including subjects who received either control for drug A or control for drug B) may result in noncomparable groups if subjects

[12] In addition, sponsors of new drugs that may enter a platform trial should consider the availability of important data for previously enrolled (nonconcurrent) control subjects, such as on baseline characteristics used for drug-specific eligibility criteria.

[13] Some consent processes allow a subject to be randomized in the trial even if the subject only consents to a subset of the drugs under evaluation; under such a process, subjects should not have the potential to be randomized to drugs for which they do not consent.

[14] See the guidance for IRBs, Clinical Investigators, and Sponsors *Informed Consent* (August 2023).

who would consent to participating in the drug A substudy differ from subjects who would consent to participating in the drug B substudy.

D. Blinding to Treatment Assignment

The approach to blinding is a critical design element in any clinical trial. A double-blind trial, where the subjects, investigators, and sponsor staff are unaware of the assigned treatment, is the optimal approach to avoid bias.[15] Ensuring that subjects and investigators are completely blinded to treatment assignment (i.e., are unaware of both a subject's assigned drug-specific substudy and whether the subject is receiving a drug or the control) becomes more complex as the number of drugs with different routes of administration or dosing schedules increases. While different degrees of blinding can be achieved depending on the blinding strategy, whether the chosen approach adequately addresses the potential sources of bias is situation-dependent and informed by several factors such as the trial design choices (e.g., endpoint selection) and the stage of drug development. Given the unique challenges related to blinding in umbrella and platform trials, sponsors should discuss their proposed approach with the Agency early in their planning. This section discusses different blinding strategies and some factors sponsors should consider when proposing a strategy.

In a placebo-controlled trial, one approach is a multiple-dummy design where subjects are completely blinded to their assigned treatment arm. For example, in a trial with three drugs, a subject would receive three placebos or one drug and two placebos. In this design, there is complete blinding to both the potential study drug the subject could receive (i.e., to the drug-specific substudy) and to whether the subject is receiving an investigational drug or a placebo. A strategy that achieves complete blinding does the best job of mitigating potential bias.

Another approach is to use a distinct, blinded placebo control for each drug where subjects have knowledge of their assigned drug-specific substudy but are blinded to whether they are receiving the given drug or its matched placebo (i.e., partial blinding). In this case, subjects could be first randomized to one of the drug-specific substudies for which they are eligible and then randomized to either that drug or its matched placebo (e.g., see Appendix section B.).

In an active-controlled trial, blinding could be implemented through a multiple-dummy approach to achieve complete blinding or a double-dummy approach for each substudy, if necessary,[16] to achieve partial blinding to whether the subject is receiving the investigational drug or the active control product. For the partial blinding approach, subjects could be first randomized to a drug-specific substudy (among those they are eligible for) and then randomized to either: (1) that drug + the placebo for the active control or (2) the matched placebo for the drug + the active control.

As the number of drugs evaluated under the master protocol increases, it may be both appropriate and more feasible to use a partial blinding strategy. However, if the primary analysis for a drug is based on a comparison to the shared control group of subjects receiving different matched controls, it is critical to consider whether this strategy adequately addresses sources of potential

[15] See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (September 1998).

[16] A double-dummy would be necessary for drug-specific substudies evaluating a drug that differs from the active control in route and/or frequency of administration.

bias for the main outcomes of interest. This strategy mitigates potential bias due to knowledge of whether the subject is receiving an investigational drug or the control. However, there is still the potential for bias if the main outcomes of interest are likely to be affected by different routes and/or schedules of administration, or by knowledge of the assigned drug-specific substudy. In trials utilizing a primary analysis with a shared control and partial blinding, a sensitivity analysis can be performed comparing each drug to only those subjects receiving the matched control. This analysis preserves the integrity of a randomized, completely blinded comparison but may be underpowered.

If there is concern about bias with a partial blinding strategy, FDA recommends the use of a multiple-dummy design to achieve complete blinding or the use of a primary analysis with comparisons for a given drug based on only its matched control. Another option might be to restrict the master protocol to only evaluate products with similar routes and schedules of administration.

A final option is to use an open-label design. Only in rare circumstances can this be justified and viewed as an adequate and well-controlled trial, for example, if the endpoint is both objective and unlikely to be influenced by differences in supportive care or subject behavior caused by knowledge of treatment assignment and if blinding is highly impractical. Sponsors should consult with FDA before considering this approach.

E. Adaptive Design

Master protocols often include adaptive design elements, such as interim analyses to potentially stop enrollment in a substudy of a drug due to efficacy or futility, to modify the sample size, and/or to modify the randomization ratio. The important principles discussed in the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019) are generally applicable to adaptive designs for master protocols. However, incorporating adaptive design elements into a master protocol can present some unique challenges. For example, consider an umbrella or platform trial with an interim analysis based on blinded pooled data to re-estimate the sample size needed to ensure adequate power to detect an effect. Conducting the analysis separately for each drug-specific substudy based on pooled data across that drug and the shared control arm may result in dissemination of information about the comparative efficacy of the drugs, particularly if the drugs entered the trial around the same time (see section IV.). In contrast, conducting the analysis based on pooled data across all the drug arms and the control arm would better protect confidentiality of interim results, but this approach may provide less accurate estimates of the sample size needed to ensure adequate power for the evaluation of each drug.

F. Multiplicity

Master protocols have multiple comparisons involving the primary endpoint; however, FDA generally does not recommend the use of multiplicity adjustments to strongly control the probability of making at least one type I error across the multiple comparisons of different drugs to the control in an umbrella or platform trial. Such comparisons of different drugs to the control are aligned with distinct clinical objectives that would typically be evaluated in multiple

independent clinical trials without adjustments for multiplicity across the trials. Furthermore, while the probability distribution for the number of type I errors[17] differs depending on whether multiple drugs are evaluated in independent trials or in a single trial (i.e., a platform or umbrella trial) with a shared control group (Proschan and Follmann 1995), the expected total number of type I errors is the same in the two scenarios due to the linearity of expectation.[18] Additionally, due to the correlation between hypothesis test statistics for different drugs in a platform or umbrella trial, the overall probability of committing at least one type I error is lower than when there are separate comparisons in independent trials. However, that same correlation can lead to an increased chance of multiple type I errors (e.g., Howard et al. 2018). Therefore, the probability distribution for the number of type I errors should be considered both in evaluating a proposed design and analysis plan and in evaluating the persuasiveness of results. For example, as noted in section III.A, use of a randomization ratio other than equal allocation to have a greater proportion of subjects in the control group may be considered to reduce the chance of multiple correlated erroneous findings (and to optimize power).

There may be some exceptions where there are different recommendations related to handling multiplicity, in particular, when multiple products being evaluated under the umbrella or platform trial are very closely related. For example, it is generally important to control the type I error probability across the evaluation of multiple doses, administrations, or formulations of the same drug, as such comparisons represent closely related questions about the same molecular entity. Evaluations of fixed-combination drug products also may have unique considerations, such as an expectation that the trial demonstrates contributions of each of the components to satisfy FDA regulations on fixed-combination prescription drugs for humans.[19]

In addition, while FDA does not generally recommend controlling for multiplicity across comparisons of different drugs to the control, it is important to control the familywise type I error probability for each individual drug across other sources of multiplicity (e.g., multiple endpoints), just as in trials that are not umbrella or platform trials.[20] There are also other important factors (e.g., the clinical relevance of the endpoint and estimated treatment effect, the quality of design and conduct, the magnitude of the p-value, and information from relevant external studies) in evaluating the evidence of effectiveness of a drug beyond the results of hypothesis testing in a single trial (e.g., a substudy of an umbrella or platform trial).[21]

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[17] Consider an example setting in which three drugs are being evaluated. Under the global null hypothesis that all three drugs are ineffective, the analyses of the trial(s) conducted could lead to false conclusions of efficacy for none of the drugs, one drug, two drugs, or all three drugs (i.e., could lead to zero, one, two, or three type I errors). The probability distribution for the number of type I errors refers to the probabilities of each of these outcomes.

[18] The linearity of expectation is the property that the expected value of the sum of random variables is equal to the sum of their individual expected values, regardless of whether the random variables are independent or dependent. Given this property, for any point in the null hypothesis (i.e., the global null scenario where all drugs are ineffective or a scenario where some drug(s) are ineffective and some drug(s) are effective), the expected number of type I errors would be equivalent.

[19] See 21 CFR 300.50.

[20] See the guidance for industry *Multiple Endpoints in Clinical Trials* (October 2022).

[21] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

G. Comparisons Between Drugs

In an umbrella or platform trial evaluating multiple drugs, the primary focus of the trial is to evaluate the efficacy and safety of each individual drug as compared to the control arm; however, there may also be interest in comparing drugs with each other. While FDA does not require such comparisons, they may be useful for comparative effectiveness research and informing treatment guidelines. Sponsors planning on conducting these comparisons should prespecify them in the statistical analysis plan.

Additionally, sponsors should consider the potential for nontransitivity in comparisons. Even if all comparisons are based on the same concurrently randomized control and drugs enter the study at the same time, certain analyses can lead to counterintuitive nontransitive results. For example, there could be a scenario in which drug A is superior to drug B, drug B is superior to drug C, and drug C is superior to drug A (e.g., Brown and Hettmansperger 2002). Nontransitivity can make it challenging to use the analysis to order treatment groups and may happen with Wilcoxon rank tests, log-rank tests, or proportional odds or Cox regressions that are fit for each pairwise comparison. Nontransitivity can occur when outcome distributions in treatment groups cannot be stochastically ordered (e.g., crossing survival curves). It generally does not occur with population summary measures such as comparisons of response rates for binary endpoints, comparisons of averages, comparisons of quantiles such as medians, or comparisons of other summary measures based on first reducing the outcome distribution in each group to a single number.

H. Safety

As noted in Section II, a development program may include both master protocols and stand-alone trials. An individual drug development program needs to provide sufficient safety data at the time a marketing application is submitted to demonstrate that the drug is safe, which requires a showing that the drug's benefits for a particular indication outweigh its risks.[22] The data from a master protocol can be considered as part of the overall safety database and benefit-risk assessment but data from additional sources may be needed to support approval. The size and duration of the safety database and approach for evaluating safety, including the use of standard adverse event definitions, toxicity grading, and data collection to allow for integrated safety analyses, should be discussed with the relevant review division. FDA encourages these discussions as safety and benefit-risk considerations for individual development programs will be drug- and disease-specific.[23]

The type of master protocol and drugs expected to be evaluated will impact the approach to safety data collection. For example, some safety outcomes (e.g., injection site reactions) may be expected to differ depending on the route and/or schedule of administration. In such circumstances, it would be appropriate for the analysis of these specific safety outcomes for a given drug to utilize only the control subjects receiving a placebo with a matched route and/or schedule of administration. If such analyses are not sufficient to evaluate these safety outcomes, sponsors may need to consider a multiple-dummy, complete blinding approach (see section

[22] See the draft guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (September 2021).

[23] See the guidance for industry *Premarket Risk Assessment* (March 2005).

III.D) or a design with greater allocation to each matched control and also may need to provide additional data from studies outside of the master protocol.

In settings where the safety profile of the drug(s) is well established, sponsors may wish to pursue a selective approach to safety data collection.[24] In a master protocol with selective safety data collection for some but not all drugs that share a control arm (e.g., with partial blinding to treatment assignment), the comparisons for a given drug should utilize only the subset of subjects in the control group for whom the appropriate safety data were planned to be collected. Additionally, if the safety data collection strategy differs between some treatment arms (e.g., differs between substudies), sponsors should address the impact of such differences in their risk-based monitoring plans given the increased potential of data collection errors.[25]

IV. CONSIDERATIONS ON TRIAL OVERSIGHT, DATA SHARING, AND DISSEMINATION OF INFORMATION

The use of shared oversight committees may result in a need for fewer resources and allow for standardization of various aspects of the trial conducted under the master protocol. Oversight committees ensure the protection of trial subjects and promote trial integrity. FDA recommends a central institutional review board (IRB) to review the master protocol, informed consent, and other relevant documents associated with trial monitoring. FDA also recommends that the sponsor appoint an independent, external data monitoring committee (DMC) or other appropriate independent entity to oversee accumulating safety and efficacy data.[26] Depending on the trial design, the sponsor may decide to have an endpoint assessment or adjudication committee to review data on important efficacy and/or safety endpoints in the trial.

Inadvertent dissemination of information from an ongoing trial conducted under a master protocol may pose a risk to trial integrity. For example, in an event-driven umbrella or platform trial in which multiple drugs enter the study at the same time, the fact that one drug versus control comparison has reached the target number of events for the final analysis could imply that other drugs still in the trial have had fewer events. If the endpoint represents the time to an event capturing a poor outcome (e.g., time to death) and the trial reports that the first drug is superior to the control, this could suggest that a drug remaining in the trial is also superior to the control because it has had even fewer events of poor outcomes. Conversely, if the endpoint represents the time to an event capturing a good outcome (e.g., recovery) and the trial reports futility for the first drug, this could suggest futility for a drug still under evaluation in the trial because it would have had even fewer events of good outcomes. This dissemination of information could potentially impact trial conduct and integrity by affecting recruitment, adherence, retention, or crossover. As another example, consider a case in which unblinded comparative results are reported for one drug in an umbrella or platform trial while another drug

[24] See the guidance for industry *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials* (December 2022).

[25] See the guidances for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013) and *A Risk-Based Approach to Monitoring of Clinical Investigations, Questions and Answers* (April 2023).

[26] See the guidance for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

remains under evaluation. If a shared control group is used, knowledge of blinded pooled data for the drug still in the trial (i.e., pooled across the drug and shared control groups) in addition to the comparative results reported for the first drug may lead to partial unblinding of comparative results for the drug still being evaluated. Hence, it may be important to limit access to these pooled data if results are to be reported for other drugs with overlapping control groups.

In general, the DMC and study team should carefully consider data access plans and how best to plan analyses and communicate results for individual drugs without leading to inadvertent dissemination of information for other drugs. Steps to maintain trial integrity should be proposed and discussed with the Agency at the design stage.

FDA also recommends that sponsors consider entering into data-sharing agreements to allow for leveraging of information across drugs. Available data on other drugs evaluated under a master protocol can add information relevant for the assessment of a specific drug. For example, leveraging information across multiple related drugs with similar mechanisms of action can improve the understanding of specific types of adverse reactions related to that mechanism. In addition, the availability of data can enable comparisons between drugs (see section III.G).

However, the leveraging of data from other drugs still under ongoing evaluation necessitates some degree of access to unblinded interim results. This access to unblinded data has the potential to negatively affect trial conduct (e.g., recruitment, adherence, or retention); therefore, such approaches should be considered only in conjunction with a careful data access plan to maintain trial integrity. A data access plan should include steps to limit, to the maximum extent possible, those with access to unblinded interim results for drugs that remain active in the master protocol. In some cases, the risks to trial integrity may outweigh the potential advantages of leveraging data from other drugs.

V. CONSIDERATIONS TO SUPPORT REGULATORY REVIEW

This section of the guidance provides regulatory considerations and recommendations for the submission of documentation to FDA for umbrella and platform trials that are intended to contribute to a demonstration of safety and substantial evidence of effectiveness. The regulatory considerations for a master protocol have increased complexity compared to those for a protocol for a stand-alone trial given the involvement of additional stakeholders, the potential for frequent changes, and the quantity of documentation. Because of these complexities, each master protocol should be submitted as a new IND to FDA.

A. General Investigational New Drug Considerations

Master protocol sponsors should take the following general considerations into account when submitting a master protocol IND:

- A master protocol sponsor should request a pre-IND meeting to discuss the protocol and submission details.[27] The cover letter for these meeting requests should clearly state "REQUEST FOR MEETING-MASTER PROTOCOL (Meeting Type B)."

- The master protocol IND should only include information regarding the master protocol trial and its substudies. A clinical investigation using a master protocol should be conducted under the master protocol IND only.

- INDs containing master protocols are subject to all applicable requirements under 21 CFR 312.

- The drugs to be evaluated in master protocols designed to contribute to a demonstration of substantial evidence of effectiveness are expected to have undergone previous clinical testing in humans and, therefore, to have a separate IND file. In rare cases where there may not be a separate IND for the drug (e.g., a drug developed solely outside of the United States), master protocol sponsors should consult FDA.

- Most clinical investigations using master protocols will be required to be conducted under an IND; however, a clinical investigation using a master protocol may be exempt[28] from this requirement in select circumstances. For example, if all the substudies of a master protocol meet the criteria for an IND exemption under 21 CFR 312.2(b)(1), the clinical investigation using a master protocol is exempt from the requirement to be conducted under an IND.

    - If an IND is not submitted for a master protocol because the clinical investigation is exempt and, subsequently, changes are anticipated that would render the clinical investigation no longer exempt from the requirement for an IND,[29] the master protocol sponsor should submit an IND before making those changes.

    - If *any* of the substudies of a master protocol do not meet the IND exemption criteria, the clinical investigation using the master protocol must be conducted under an IND.[30]

- The master protocol sponsor should provide a separate Investigator's Brochure (IB) for each drug being evaluated in the master protocol rather than a single IB that covers all the drugs being evaluated.

[27] See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017).
[28] See the guidance for clinical investigators, sponsors and IRBs *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND* (September 2013).
[29] For example, when there is an addition of a new arm in a platform trial that does not meet exemption criteria.
[30] See 21 CFR 312.2.

B. IND Cross-Referencing

FDA review of investigational drugs evaluated in a master protocol will typically need to rely on previously submitted information about the individual drugs. The following should be considered regarding cross-references between the master protocol and individual drug INDs:

- The master protocol, in its entirety, should not be incorporated into other INDs via cross-reference.

- Individual drug INDs for drugs being evaluated in a master protocol can cross-reference limited elements of the master protocol IND (e.g., the drug-specific substudy).

- The master protocol IND should cross-reference information in the INDs for the individual investigational drugs, such as nonclinical study findings, drug product quality specifications, and clinical data.

- To cross-reference information in another sponsor's IND, a signed, written statement from that sponsor authorizing such cross-reference must be provided.[31]

C. Protocol Amendments

Given the potentially rapid pace of changes associated with master protocols, FDA recommends the following procedures regarding protocol amendments:

- A new drug proposed for evaluation (i.e., a new substudy) in the master protocol should be submitted as a protocol amendment to the master protocol IND.

    - For master protocols submitted electronically, FDA requires that Study Tagging Files be used to identify the master protocol and each of its substudies. Relevant documentation under the master protocol and each substudy must use appropriate file-tags (e.g., protocol and/or amendment, study report body). Use of the Study Tagging File will improve the organization of the electronic common technical document (eCTD) and facilitate FDA's review of the submissions (see Figure B.).[32]

- The master protocol sponsor should clearly mark the cover letter for protocol amendments with "Protocol Amendment-MASTER PROTOCOL," and include a clean and track changes version of the document as well as a document specifying what changes are being made.

    - FDA recommends that the cover letter include updates on the status of each drug in the master protocol.

[31] See 21 CFR 312.23(b).

[32] Additional information on eCTD submission standards can be found at: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

- The master protocol sponsor should submit protocol amendments that substantively affect the safety, quality, or scope of the master protocol at least 30 days before initiation of the changes. For example, to add a new drug to the master protocol, the master protocol sponsor should submit the protocol amendment at least 30 days before initiation of that substudy.

- The master protocol sponsor should notify the regulatory project manager at least 48 hours before submitting any protocol amendment that could substantively affect the safety, quality, or scope of the master protocol.

D. Communications and Safety Reporting

The master protocol IND should include a well-designed communication plan to ensure timely and effective communications between many stakeholders and help ensure compliance with legal requirements. FDA recommends that a communication plan be employed by the master protocol sponsor to ensure the dissemination of information and advice from FDA to the individual drug sponsor(s). Additionally, the master protocol sponsor should establish a systematic approach that ensures the rapid communication of serious safety issues to clinical investigators and FDA under IND safety reporting regulations.[33] This should include a process for rapid implementation of protocol amendments to address serious safety issues.[34] With regard to safety reporting, sponsors should be aware of the following:[35]

- All clinical investigators are required to submit safety reports to the master protocol sponsor.[36]

- Master protocol sponsors are required to submit IND safety reports to FDA *and* all participating investigators when they determine that a serious adverse event is unexpected, and there is a reasonable possibility that the drug caused the serious adverse event (i.e., there is evidence to suggest a causal relationship between the drug and the adverse event).[37]

[33] See 21 CFR 312.32.

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

[35] For additional information regarding safety reporting, see the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012). Also, see the draft guidance for industry *Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[36] See 21 CFR 312.64(b)). Also, see the guidance for industry *Investigator Responsibilities-Safety Reporting for Investigational Drugs and Devices* (September 2021).

[37] See 21 CFR 312.32(c)(1). Sponsors are also required under 21 CFR 312.55(b) to keep each participating investigator informed of any new observations discovered or reported to the sponsor on the drug, particularly with respect to adverse events and safe use.

- FDA expects that the master protocol sponsor will also forward all initial IND safety reports to the relevant individual drug sponsors. Those sponsors in turn, are required to promptly review the information.[38]

    - The individual drug sponsor should review each safety report, add any relevant context or additional information, and submit a modified report to their active IND(s) for the investigational drug, if required,[39] as a follow-up safety report[40] that references the initial IND safety report submitted by the master protocol sponsor.

VII. REFERENCES[41]

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[38] See 21 CFR 312.32(b).
[39] See 21 CFR 312.32(c)(1).
[40] See 21 CFR 312.32(d).
[41] Some of the listed references also apply to the Appendix.

VI. APPENDIX[1]

A. Optimal Allocation Ratio

In certain scenarios, such as trials to evaluate more than two treatment groups compared to a common control, unequal allocation can improve efficiency (Chandereng et al. 2020). Here is a derivation in a simple case that power can be increased with disproportionately greater randomization to the control group in an umbrella or platform trial with a fixed total sample size. Consider an umbrella trial in which there are N total subjects, k drugs, and 1 control group. For some fraction p suppose that $N \times p$ subjects are assigned to control and $N \times (1-p)/k$ subjects are assigned to each drug. Also, suppose that the treatment effect δ is the same for each drug and that outcomes for all groups have the same variance. The power of a z-test is determined by δ/σ, where σ^2 is the variance of the (treatment – control) difference in means and is proportional to $f(p) = 1/[N \times (1-p)/k] + 1/(N \times p)$. Considering p as continuous in $(0, 1)$ (even though strictly speaking the number of treatment and control subjects should be integers) the first derivative of $f(p)$ is $1/N \times [k/(1-p)^2 - 1/p^2]$. The second derivative of $f(p)$ is $1/N \times [2 \times k/(1-p)^3 + 2/p^3] > 0$, so the function $f(p)$ is convex, and thus variance is minimized by setting the first derivative to zero. This is achieved at $p = 1/(1+\sqrt{k})$ which is equivalent to a randomization ratio for the control relative to a given drug of $\sqrt{k}$: 1. In contrast, equal allocation to all treatment groups would correspond to $p = 1/(1+k)$. This example illustrates a simple case, and the Chandereng et al. 2020 paper shows more generally, that the optimal allocation will have disproportionate randomization to the control group when $k > 1$.

The intuitive reason why power can increase with disproportionate randomization is that it can lead to a larger sample size for each (drug – control) comparison, and the power with an unequally randomized large sample size comparison can in some cases exceed the power of an equally randomized small sample size comparison. Consider an example under the paradigm above where the total sample size for the master protocol is fixed at 600 subjects and there are 4 drugs and 1 shared control group. Optimal allocation of 200 subjects ($p = 1/3$) to the shared control group and 100 subjects to each drug group would result in 300 subjects and optimal power for the comparison of a given drug to the control group. Equal allocation to all groups ($p = 1/6$) would result in 120 subjects allocated to each drug group and to the control group, resulting in only 240 subjects for the comparison of a given drug to the control group.

B. Examples of Randomization Strategies for Partially-Blinded, Placebo-Controlled Studies

<u>Example 1: Randomization Process for 1:1 Allocation Ratio</u>

Here is one example of a 2-step randomization process that maintains a 1:1 allocation ratio for the pooled placebo arm relative to a given drug:

1. Randomize with equal probability (1: 1: ... : 1) to one of the drugs the subject is eligible to receive

[1] The references cited in the Appendix are listed in the References section of the guidance.

2. Randomize to the drug or matching placebo version of that product with allocation k: 1, where k is the number of drugs for which the subject is eligible

There are alternative randomization strategies that also target a 1:1 allocation ratio for a given drug and the pooled placebo arm. One alternative strategy is to first randomize subjects to one of the drugs or the pooled placebo arm with equal probability, and then randomize subjects in the pooled placebo arm to one of the drug-specific placebos with equal probability. A second alternative strategy is to first randomize subjects to drug or placebo in a k: 1 ratio, and then randomize subjects to a specific drug or drug-specific placebo with equal probability.

Example 2: Randomization Process for $\sqrt{k}$: 1 Allocation Ratio

Here is one example of a 2-step randomization process that targets a $\sqrt{k}$: 1 allocation ratio for the pooled placebo arm relative to a given drug, intended to increase power with greater-than-equal allocation to placebo (see Appendix: section A):

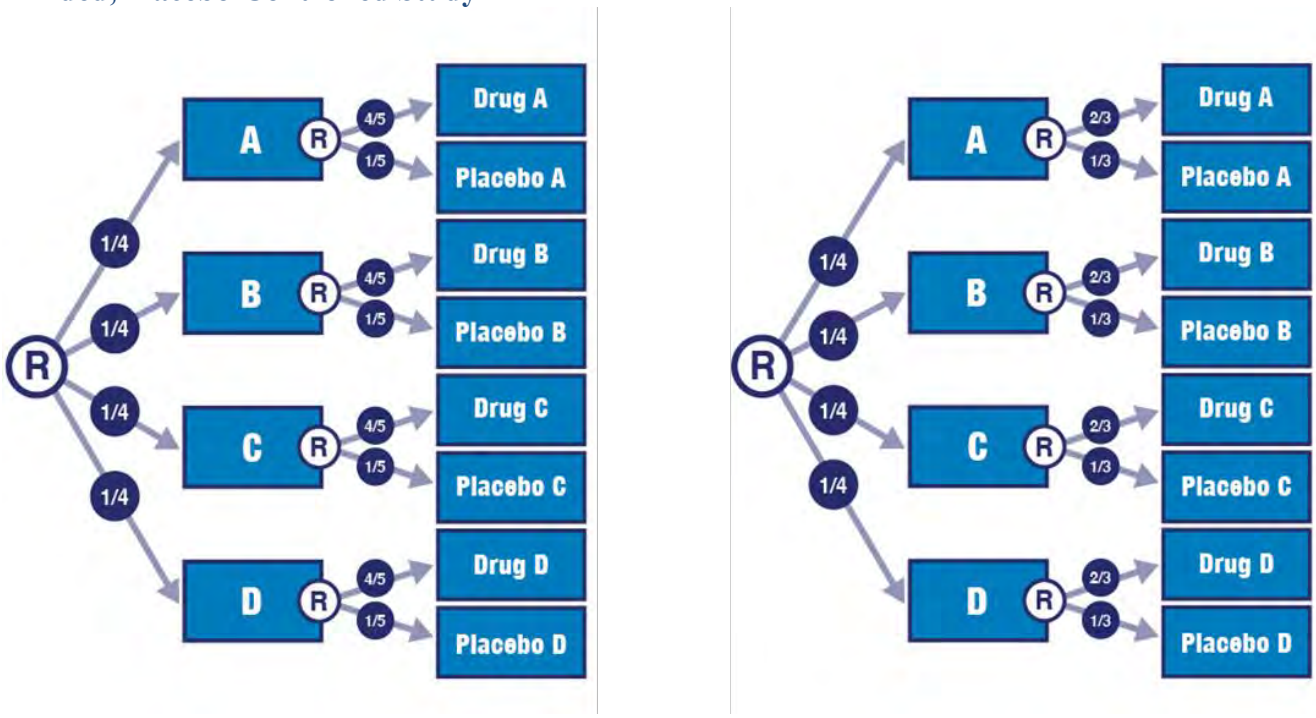
1. Randomize with equal probability (1: 1: ... : 1) to one of the drugs the subject is eligible to receive

2. Randomize to the drug or matching placebo version of that product with allocation $\sqrt{k}$: 1, where k is the number of drugs for which the subject is eligible

Illustrative Figure and Table

The following figure illustrates the two example randomization processes described above in a trial with four drugs for a subject who is eligible to receive all four drugs. The following table describes key randomization probabilities and ratios for these examples.

Figure A: Schematic to Illustrate Examples of Randomization Processes for a Partially-Blinded, Placebo-Controlled Study



Left (Example 1): 1:1 allocation ratio for the pooled placebo arm relative to a given drug
Right (Example 2): $\sqrt{k}$: 1 allocation ratio for the pooled placebo arm relative to a given drug

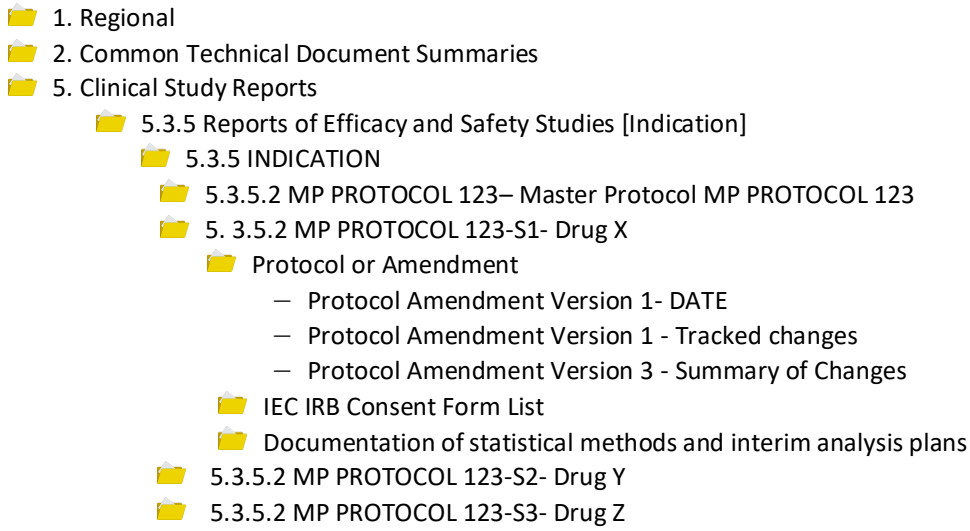
Table A: Randomization Probabilities and Ratios for Examples of Randomization Processes for a Partially-Blinded, Placebo-Controlled Study

	Example 1	Example 2
Allocation ratio for the pooled placebo arm relative to a given drug	**1:1**	$\sqrt{\boldsymbol{k}}$**: 1**
Example calculations with four drugs (i.e., $k = 4$)		
Randomization probability		
Individual drug (e.g., drug A)	$\frac{1}{4} \times \frac{4}{5} = \mathbf{\frac{1}{5}}$	$\frac{1}{4} \times \frac{2}{3} = \mathbf{\frac{1}{6}}$
Individual placebo (e.g., placebo A)	$\frac{1}{4} \times \frac{1}{5} = \mathbf{\frac{1}{20}}$	$\frac{1}{4} \times \frac{1}{3} = \mathbf{\frac{1}{12}}$
Pooled placebo	$4 \times \frac{1}{4} \times \frac{1}{5} = \mathbf{\frac{1}{5}}$	$4 \times \frac{1}{4} \times \frac{1}{3} = \mathbf{\frac{1}{3}}$
Any drug	$4 \times \frac{1}{4} \times \frac{4}{5} = \mathbf{\frac{4}{5}}$	$4 \times \frac{1}{4} \times \frac{2}{3} = \mathbf{\frac{2}{3}}$
Randomization ratio		
Pooled placebo: Individual drug (e.g., pooled placebo: drug A)	1:1	2: 1 ($\sqrt{4}$: 1)
Individual placebo: Individual drug (e.g., placebo A:drug A)	1:4	1:2

C. Example of How to Use eCTD for a Master Protocol

The figure below illustrates an example of eCTD organization for a master protocol with multiple substudies.

Figure B. eCTD of an IND with Master Protocol "MP PROTOCOL 123" and Substudies S-1, S-2, and S-3



eCTD = electronic common technical document