Master Protocols for Drug and Biological Product Development

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Scott N. Goldie at Scott.Goldie@fda.hhs.gov, or (CBER) Office of Communication, Outreach and Development, at 800-835-4709 or 240-402-8010.

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)

June 2026
Biostatistics / Clinical / Medical
Revision I

Master Protocols for Drug and Biological Product Development

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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under a master protocol as well as guidance on the submission of documentation to support regulatory review.[2] This draft guidance revises and replaces the previous draft guidance for industry of the same name issued on December 21, 2023, and reflects FDA's consideration of public comments on the draft guidance. This revision provides additional recommendations on basket trials and minor changes for clarity on topics such as randomization, choice of control, and informed consent.

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 drugs[3] in one or more diseases or conditions within the overall study structure.

- *Substudy*: the specific objectives, design, conduct, and analysis related to evaluation of a single drug in a single disease, condition, or disease subtype in the master protocol.

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

- *Umbrella trial*: a trial designed to evaluate multiple drugs concurrently for a single disease or condition. Figure 1 provides a schematic representation of an umbrella trial.

[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.

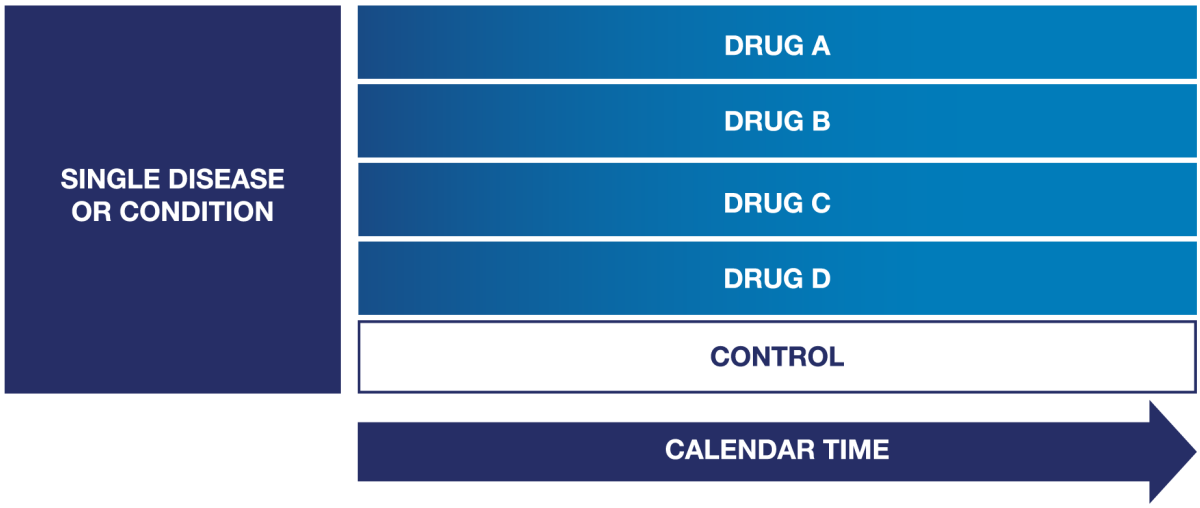
[3] For the purposes of this guidance, all references to drugs include both human drugs and biological products unless otherwise specified.

- *Basket trial*: a trial designed to evaluate a drug for multiple diseases, conditions, or disease subtypes. Figure 2 provides a schematic representation of a basket trial.

- *Platform trial*: a trial designed to evaluate multiple drugs for one or more diseases, conditions, or disease subtypes in an ongoing manner, with drugs entering or leaving the platform. Figure 3 provides a schematic representation of a platform trial evaluating multiple drugs for a single disease.

Trials using a master protocol may incorporate design features common to both umbrella and basket trials. For example, some platform trials incorporate both umbrella and basket components by evaluating multiple drugs for multiple diseases (see Figure 4 for a schematic representation). Trials using a master protocol also may evaluate individual drugs or drug combinations.[4]

Figure 1. Example of an Umbrella Trial



[4] There are additional considerations for the development of fixed-combination drugs; see 21 CFR 300.50 for more information.

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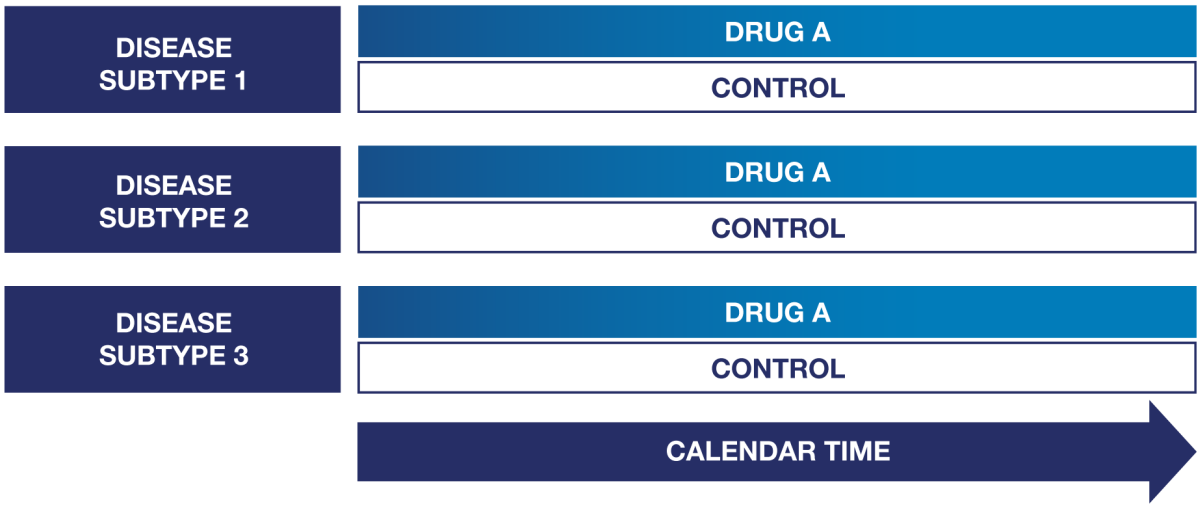
61 **Figure 2. Example of a Basket Trial**



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64 **Figure 3. Example of a Platform Trial in One Disease**

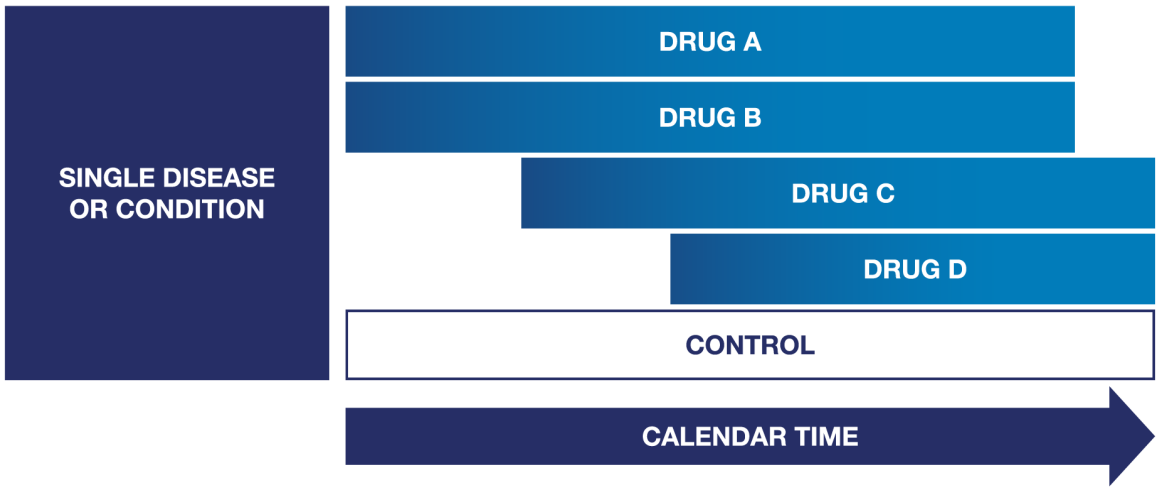

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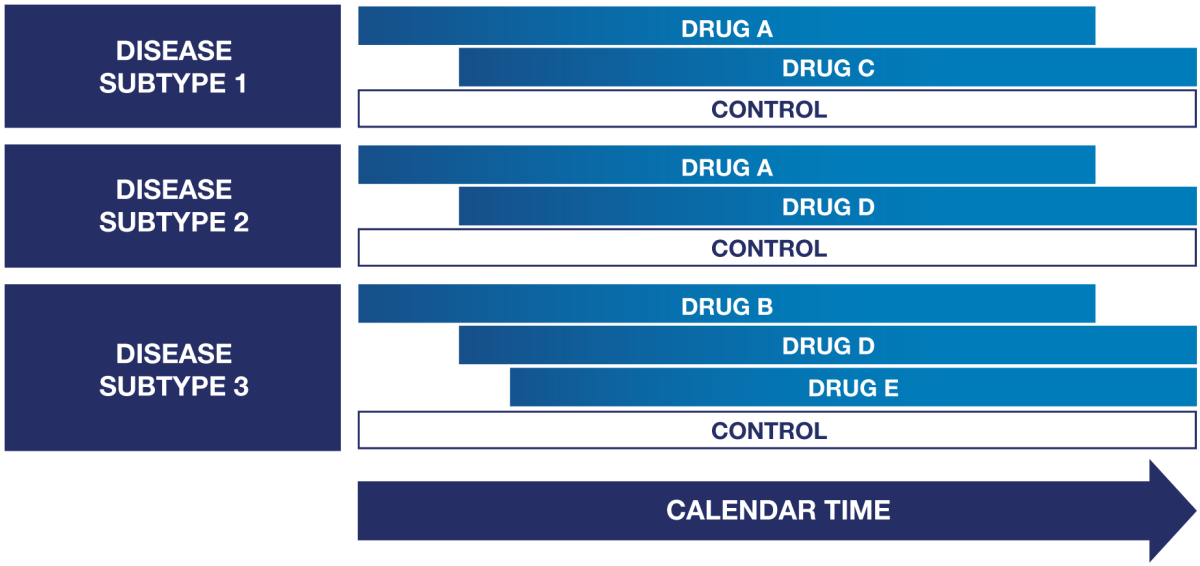
Figure 4. Example of a Platform Trial in Multiple Diseases



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.[5] A master protocol should be submitted in a new Investigational New Drug Application (IND) to FDA (see section V). In many instances, individual drugs chosen for evaluation in the master protocol will also be evaluated under separate 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 trials using a master protocol that are intended to contribute to a demonstration of safety and substantial evidence of effectiveness of a drug. The concepts discussed may also be useful to consider for early-phase or exploratory trials under a master protocol as well as those conducted to satisfy post-marketing commitments or requirements. The recommendations and considerations in this guidance may 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.[6]

[5] See 21 CFR 312.3.

[6] This guidance does not address first-in-human expansion cohort studies in oncology, because 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). 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 considerations in this guidance apply to a range of therapeutic areas. 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 the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

When well-designed and well-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 logistical advantages by leveraging shared protocol elements (e.g., visit schedule, measurement procedures), shared infrastructure (e.g., recruitment efforts, a network of clinical sites, central facilities, a central randomization system, an overarching data management system), and shared oversight (e.g., by a steering committee and data monitoring committee). Some master protocols may also improve efficiency by using a shared control arm in evaluating multiple drugs or by leveraging information on drug effects across multiple related diseases, conditions, or disease subtypes. Such advantages may make master protocols particularly suitable in certain settings. For example, a master protocol may be useful in settings where participant recruitment is challenging (e.g., some pediatric or rare-disease trials), because comparing multiple drugs to a shared placebo arm can reduce the number of participants on placebo relative to multiple trials comparing each drug to a placebo.

However, master protocols add elements of complexity, which can increase start-up time and present design challenges (for example, in ensuring adequate blinding to treatment assignment (see section III.D)). Additionally, master protocols involving multiple interested parties 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, because this will inform its objectives, design, and analysis plan. For example, the choice of endpoint in a master protocol may differ depending on whether the objective is to screen multiple drugs rapidly to determine which ones to carry forward into later stage trials or 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

[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.

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 FOR DESIGN AND ANALYSIS

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

A. Randomization

FDA recommends randomization of participants to the drug (or to one of the drugs) being evaluated or to a control arm to remove systematic imbalances between treatment arms in both measured and unmeasured prognostic factors and to ensure reliable inference on drug safety and effectiveness.

In master protocols evaluating multiple drugs with a shared control arm, sponsors should consider using a randomization scheme that allocates more participants 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 participant 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.H).

The choice of a randomization scheme can be informed by multiple factors, including efficiency and operational considerations. Randomization schemes that maintain a constant randomization ratio between each drug and control can be considered. It is also possible to design a trial such that the randomization ratio changes over time. This can occur when drugs 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. Another randomization scheme could maintain a constant probability of being randomized to control over time, such that the randomization ratio for an individual drug relative to control changes as the number of drugs evaluated in the platform trial changes. If the randomization ratio for a drug relative to the control changes over time, the comparisons between the drug and control should account for time periods of different randomization ratios.

[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.

Possible approaches include stratifying by the time period or inverse weighting by probabilities of treatment assignments. Such approaches are important to prevent the potential for bias due to temporal trends, for example, if participants enrolled earlier in the trial are both more likely to have favorable outcomes and more likely to be assigned to drug.

In settings where it is reasonable for a participant to be treated simultaneously with more than one of the drugs being evaluated under a master protocol, a factorial design could also be considered. For example, participants 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 participants 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 evaluating multiple drugs to use drug-specific eligibility criteria in some settings (e.g., excluding participants with diminished kidney function for a drug with kidney toxicity). In these situations, protocols and randomization processes should be designed to prevent participants from being randomized to drugs they are not eligible to receive, as this would compromise participant safety and the integrity of the randomized comparison (see additional discussion in section III.B).

It may be reasonable in some master protocols for participants who complete one drug-specific substudy and an appropriate washout period to re-enroll and be randomized to a different drug-specific substudy. This is similar to stand-alone trials, in which participants who previously completed a clinical trial may be eligible to enroll in a new clinical trial of a different drug after an appropriate washout period. However, there may be additional considerations in some master protocols, such as the importance of accounting for correlated data within participants who receive control in one substudy and drug in another substudy of a master protocol (see 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. Although 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]

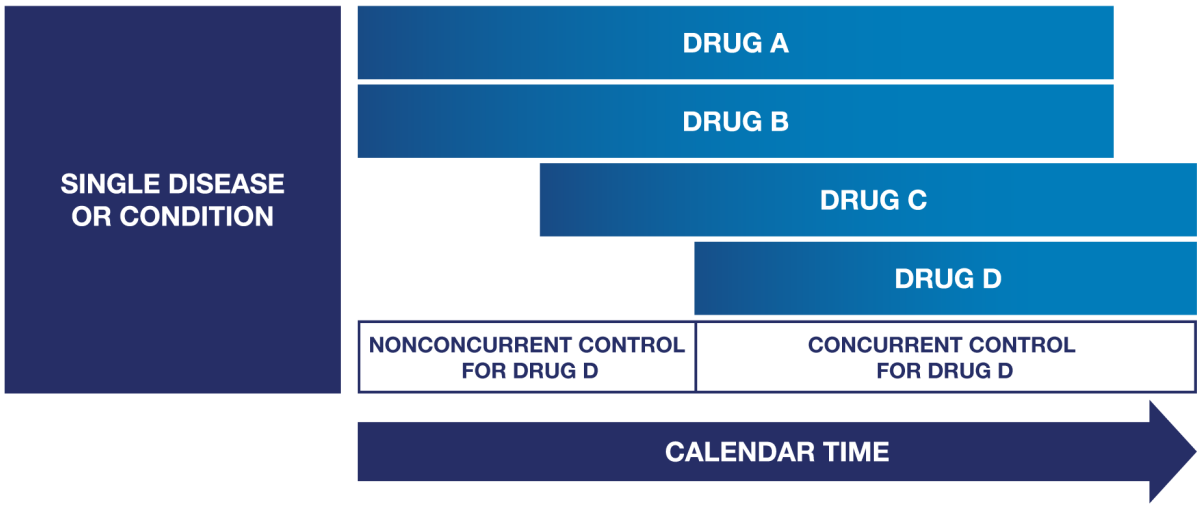
[9] The control could be placebo or active and could be used for superiority and/or non-inferiority comparisons. General considerations about the choice of control, such as those discussed in the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001),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

Types of Control Data

The composition of the control group for a given drug is an important consideration in platform and umbrella trials. 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 participants randomized to the control who were concurrently enrolled (i.e., enrolled during the time period when participants were being randomized to the given drug) and participants who were nonconcurrently randomized to the control and thus could not have been randomized to the given drug. For example, consider a platform trial that initially randomizes participants 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 5 illustrates such a hypothetical platform trial and depicts concurrent and nonconcurrent controls for the evaluation of drug D.

Figure 5. Schematic of a Platform Trial that Depicts Concurrent and Nonconcurrent Controls for the Evaluation of a Given Drug (Drug D)



It is also possible for an umbrella or platform trial evaluating multiple drugs to include participants who are enrolled concurrently with a given drug but who could not have been randomized to that drug. This scenario can occur for multiple reasons. For example, a substudy may contain drug-specific eligibility criteria for safety reasons (e.g., exclusion of participants with diminished kidney function for a drug with kidney toxicity). Similarly, participants may be unable to receive a drug when they are enrolled in a master protocol in which some sites (e.g., in different geographical regions) offer only a subset of the drugs currently under evaluation.

Recommended Use of Control Data to Preserve Integrity of Randomized Comparisons

The control group used for the primary comparison of any given drug in a master protocol evaluating multiple drugs should generally be selected to preserve randomization and include only concurrently eligible control participants (i.e., only those participants who met the drug eligibility criteria and could have been randomized to the given drug but were instead concurrently randomized to the control arm). Nonconcurrently randomized participants and

concurrently randomized participants who could not have been randomized to the drug should not be included.

Use of concurrently eligible controls preserves the integrity of randomized comparisons and ensures valid inference on the effects of the drug by avoiding systematic differences between groups with respect to both known and unknown factors that are prognostic of the key outcomes. For example, systematic differences between a drug and nonconcurrent control could be caused by temporal shifts in participant 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 use only concurrently eligible controls.

Alternative Approaches

Although use of a concurrently eligible control group is the preferred approach to support the most robust conclusions, there may be rare circumstances in which sponsors can justify use of other control data. Use of other control data, such as nonconcurrent control data, can increase the precision of inference on the treatment effect due to the increased number of participants in the control arm. This increased precision 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 in their planning. Information relevant to this discussion includes: 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 used; the expected separation in calendar time between randomization of nonconcurrent control participants and initiation of randomization to the drug of interest; and statistical methods intended to account for potential temporal changes and their underlying assumptions.

In 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 before the start of the trial, as this will avoid a scenario where a sponsor proposes to use nonconcurrent data after seeing certain 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 participants entering a trial may change over time. For example, participants entering a trial at the beginning may be more likely to have had the disease for a longer period of time and thus a worse prognosis than participants 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. Possible approaches 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),[13] and/or a network meta-analysis to combine comparisons between concurrently randomized treatment arms. The underlying assumptions of the primary 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.

Similar considerations apply to the inclusion in the analysis of participants who are enrolled and randomized to the control concurrently with the given drug but who could not have been randomized to that drug. For example, a proposal to include concurrently enrolled participants who do not meet eligibility criteria for the given drug should be supported by a scientific justification that discusses bias-variance tradeoffs. In addition, methods should be planned to address potential bias, such as adjustment for prognostic factors that may differ between the drug arm and concurrently enrolled participants randomized to the control who do not meet drug eligibility criteria.

Changes to the Control Arm or Background Therapy

Sponsors should carefully consider 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 the integration of 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 participant could be randomized.[14] Additionally, 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

[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 participants, such as on baseline characteristics used for drug-specific eligibility criteria.

[13] For more discussion on Bayesian methods, see the draft guidance for industry *Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products* (January 2026). When final, this guidance will represent the FDA's current thinking on this topic.

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

under evaluation. FDA recognizes that the complexity of a master protocol could result in lengthy informed consent forms that are difficult for participants to understand and therefore recommends that sponsors follow approaches outlined in guidance to reduce the length and enhance the readability of the consent forms.[15]

In master protocols evaluating multiple drugs with a shared control arm, the informed consent process should occur before a participant's randomization and avoid drug-specific substudy consent. Although obtaining drug-specific substudy consent after participants have been randomized (e.g., in a two-step consent approach) may decrease the complexity of the informed consent process, it may also result in participants with different distributions of prognostic characteristics across the drug substudies, raising concern about the comparability of each drug group with the shared control group (comprised of control participants from different drug-specific substudies).

To illustrate the concern, consider a master protocol with two drugs (drug A and drug B) in which the participant consents to screening and randomization to a drug-specific substudy as part of the master protocol, with a separate drug-specific substudy informed consent process to occur after randomization to that substudy; after the consent for the drug-specific substudy, the participant is then randomized to the drug or its matched control. With this process, comparing drug A against the shared control arm (including participants who received either control for drug A or control for drug B) may result in noncomparable groups if participants who would consent to participating in the drug A substudy differ from participants who would consent to participating in the drug B substudy.

Therefore, an approach with drug-specific substudy consent adds the potential for bias. For example, if a non-trivial overall proportion of participants choose not to consent to their assigned drug-specific substudy, or if differential proportions choose not to consent across the different drug-specific substudies, it may compromise the interpretability of trial results. Sponsors considering post-randomization drug-specific study consent should provide a strong justification for doing so and a description of steps that will be taken to mitigate risk of bias (e.g., specifying that participants who do not consent to their assigned substudy are not eligible to re-enroll and be randomized to another substudy).

D. Blinding to Treatment Assignment

The approach to blinding is a critical design element in any randomized clinical trial. A double-blind trial, where the participants, investigators, and sponsor staff are unaware of the assigned treatment, is the optimal approach to avoid bias.[16]

In a master protocol evaluating multiple drugs with a shared control, ensuring that participants and investigators are completely blinded to treatment assignment (i.e., unaware of both a

[15] See the guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (August 2023). Also, see the draft guidance for sponsors, investigators, and institutional review boards *Key Information and Facilitating Understanding in Informed Consent* (March 2024). When final, this guidance will represent the FDA's current thinking on this topic.

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

participant's assigned drug-specific substudy and whether the participant is receiving a drug or the control) becomes more complex as the number of drugs with different routes of administration or dosing schedules increases. Different blinding strategies can achieve different degrees of blinding. 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, sponsors should discuss their proposed approach with the Agency early in their planning. This section discusses different blinding strategies for master protocols evaluating multiple drugs with a shared control and some factors sponsors should consider when proposing a strategy.

In a placebo-controlled trial, one approach is a multiple-dummy design where participants are completely blinded to their assigned treatment arm. For example, in a trial with three drugs, a participant would receive three placebos or one drug and two placebos. In this design, there is complete blinding to both the potential investigational drug the participant could receive (i.e., to the drug-specific substudy) and to whether the participant 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 participants 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, participants 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,[17] to achieve partial blinding to whether the participant is receiving the investigational drug or the active control product. For the partial blinding approach, participants 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 participants receiving different matched controls, it is critical to consider whether this strategy adequately addresses sources of potential bias for the main outcomes of interest. This strategy mitigates potential bias due to knowledge of whether the participant 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 using a primary analysis with a shared control and partial blinding, a sensitivity analysis can be performed comparing each drug to only those participants receiving the matched control. This analysis preserves the integrity of a randomized, completely blinded comparison but may be

[17] 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.

underpowered. Refer to section III.I for additional considerations regarding the analysis of certain safety outcomes when using a partial blinding strategy.

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. Other options might be to restrict the master protocol to only evaluate products with similar routes and schedules of administration, or to use a multiple-dummy approach and a shared control within groups of drugs with similar routes and schedules of administration (e.g., within drugs administered intravenously and within drugs administered orally).

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 participant 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 decide whether to 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 unique challenges. For example, consider an umbrella or platform trial with a binary endpoint and an interim analysis based on the blinded pooled event rate 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 the pooled event rate 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). Although conducting the analysis based on pooled data across all the drug arms and the control arm would better protect confidentiality of interim results, this approach may provide less accurate estimates of the sample size needed to ensure adequate power for the evaluation of each drug.

F. Comparisons Between Drugs

In an umbrella or platform trial evaluating multiple drugs, the primary focus is to evaluate the efficacy and safety of each individual drug compared to the control arm; however, there may also be interest in comparing drugs with each other. Although 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.

G. Approaches for Evaluating Drug Effects in Multiple Diseases, Conditions, or Disease Subtypes

Basket trials and platform trials with basket components involve the evaluation of the effects of a drug in multiple diseases, conditions, or disease subtypes in different substudies. In some cases, the primary objective may be to evaluate the average effect of the drug in the combined population by conducting a single combined analysis of data across the individual substudy populations. In other cases, the primary objective may be to evaluate the effects of the drug within each disease, condition, or disease subtype. One approach to support this objective is to conduct separate analyses within each individual substudy population using only data from that population. This may be the most appropriate approach in many basket trials to minimize bias. Alternatively, in settings where there is sufficient scientific justification, sponsors may consider leveraging information across related substudy populations to allow for potential efficiency gains. Information across substudies may be leveraged in a qualitative or quantitative manner. For example, consider a development approach to demonstrate substantial evidence of effectiveness based on one adequate and well-controlled trial and confirmatory evidence. If scientifically supported, the evaluation of the target substudy population may serve as the one adequate and well-controlled trial with the results in other related substudy population(s) in the master protocol providing the confirmatory evidence.[18] Another option would involve more quantitative leveraging of information with analyses that borrow data across substudy populations (e.g., with Bayesian methods) such that estimates of the treatment effect in a subpopulation are based on data from that subpopulation as well as data from other relevant subpopulations.

Sponsors should specify and justify a clear primary objective of the overarching trial and provide a rationale for how the design and analysis of the trial will accomplish the objective. This should include a justification for combining or leveraging information across substudies. Considerations related to combining or leveraging information across substudies include the following:

- The degree of relevance of information across substudies, i.e., the extent to which drug effects are expected to be similar across the substudy populations; this may be influenced by, for example:
    - The degree of similarity in disease pathophysiology across the substudy populations
    - The degree of similarity in how the drug is expected to modulate disease pathophysiology, including the drug's pharmacokinetic properties, across the substudy populations
    - The degree of similarity in endpoints and other estimand attributes across the substudy populations

[18] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

- The prevalence of the different substudy populations and feasibility considerations, such as the feasibility of enrolling sufficient sample sizes within individual substudy populations to support separate analyses that would be adequately powered under plausible assumptions

- Whether there will be additional late-phase trial(s) conducted to contribute to a demonstration of substantial evidence of effectiveness in the substudy populations; for example, if a substudy under a master protocol is intended to be the sole adequate and well-controlled trial providing evidence in a specific population, less combining or leveraging and more persuasive stand-alone evidence in that population may be expected

Sponsors should prespecify and justify statistical methods, including both 1) methods to evaluate the primary trial objective (e.g., hypothesis tests and associated success criteria), and 2) methods to estimate treatment effects with quantification of uncertainty. Statistical methods fall along a continuum with respect to how information is combined or leveraged across substudies. At one end of the continuum is the approach of conducting separate analyses within individual substudy populations, which involves no leveraging of information across substudy populations. At the other end of the continuum is the approach of conducting a single combined analysis of data across the individual substudy populations and evaluating the average effect in the combined populations. There are also statistical approaches that fall somewhere between the two ends of the continuum and borrow some information on drug effects in other substudy populations when evaluating drug effects in a given individual substudy population. These include methods (e.g., Bayesian hierarchical models) in which the degree of borrowing depends on the similarity in the observed effects across the substudy populations. Selecting from among the different statistical approaches involves bias-variance tradeoffs. Greater borrowing of information across substudy populations generally improves precision and may increase power, but also may increase bias in the evaluation of drug effects in a given substudy population.

Regardless of the approach used to evaluate the primary trial objective (e.g., specific hypothesis testing method), estimation of treatment effects with quantification of uncertainty within each individual substudy population is important to facilitate benefit-risk assessments. For example, if the primary hypothesis test evaluates the average effect in the combined substudy populations, subgroup analyses to estimate effects within the individual substudy populations (potentially with some borrowing, if justified) should be conducted to further inform the benefit-risk assessment in each substudy population.

Sponsors should support their proposed statistical approach with an evaluation of its operating characteristics relative to alternatives, including in scenarios where true effects differ across the substudy populations (e.g., in which the drug is only effective in one or a subset of the substudy populations). This should generally include an evaluation of probabilities of false positive and false negative conclusions (see section III.H) and bias-variance tradeoffs in estimates.

H. Multiplicity

Master protocols entail 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, or across the multiple comparisons of a single drug to control in different diseases, conditions, or disease subtypes. Such comparisons are aligned with distinct clinical objectives that would typically be evaluated in multiple independent clinical trials without adjustments for multiplicity across the trials. Furthermore, the expected total number of type I errors is the same regardless of whether these comparisons are made in independent trials or in a single trial under a master protocol, due to the linearity of expectation.[19]

There may be some exceptions where there are different recommendations related to handling multiplicity, in particular, when multiple treatments being evaluated under a master protocol 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, because 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.[20]

In addition, it is important to control the familywise type I error probability for the evaluation of each individual drug in an intended population across other sources of multiplicity (e.g., multiple endpoints), just as in trials that are not conducted under a master protocol. Different types of master protocols can also introduce unique considerations related to probabilities of false positive and false negative conclusions, as discussed below.

In master protocols evaluating multiple drugs with a shared control arm, even though the expected total number of type I errors is the same as in the case where the drugs are evaluated in independent trials, the probability distribution for the number of type I errors[21] differs (Proschan and Follmann 1995). For example, due to the correlation between hypothesis test statistics for different drugs, the overall probability of committing at least one type I error is lower, whereas the probability of multiple type I errors is higher, than when there are separate comparisons in independent trials (e.g., Howard et al. 2018). Therefore, the probability distribution for the number of type I errors (as well as other important operating characteristics, such as power) 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 participants in the control group may be considered to reduce the chance of multiple correlated erroneous findings and to optimize power.

[19] 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 (e.g., in a master protocol evaluating multiple drugs, 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.

[20] See 21 CFR 300.50.

[21] 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.

In master protocols evaluating a drug for multiple diseases, conditions, or disease subtypes in different substudies, it is important to evaluate type I error probabilities and other important operating characteristics, such as power, for the individual substudy populations. Sponsors should justify the appropriateness of the operating characteristics in a range of different scenarios. Approaches that involve borrowing information on drug effects across the different substudy populations may come with tradeoffs. For example, borrowing may lead to better operating characteristics in scenarios where true effects are similar across the substudy populations but worse operating characteristics in scenarios where effects are considerably different (e.g., where the drug is only effective in one or a subset of the substudy populations). The appropriateness of borrowing and of the resulting operating characteristics in different scenarios may depend on many factors (see further discussion in section III.G).

Finally, there are 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 in a given population beyond the results of hypothesis testing in a single trial (e.g., a substudy of a trial conducted under a master protocol).[22]

I. 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 of a marketing application to demonstrate that the drug is safe, which requires a showing that the drug's benefits for a particular indication outweigh its risks.[23] The data from a master protocol can be considered as part of the overall safety database and benefit-risk assessment. As with all development programs, data from other sources (e.g., human safety data from other clinical investigations, pharmacology/toxicology studies) will be needed to support approval.[24] 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 because safety and benefit-risk considerations for individual development programs will be drug- and disease-specific.[25]

The type of master protocol and drugs expected to be evaluated will influence the approach to safety data collection and analysis. For example, in a master protocol evaluating multiple drugs with a shared control and partial blinding, some safety outcomes (e.g., injection site reactions) may be expected to differ depending on the route and/or schedule of administration of the drugs being evaluated. In such circumstances, it would be appropriate for the analysis of these specific safety outcomes for a given drug to use only the control participants receiving a placebo with a matched route and/or schedule of administration. If such analyses are not sufficient to evaluate

[22] 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.

[23] See the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023).

[24] See 21 CFR 314.50.

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

these safety outcomes, sponsors may need to consider a multiple-dummy, complete blinding approach (see section 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.[26] 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 use only the subset of participants 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.[27]

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

Oversight committees ensure the protection of trial participants and promote trial integrity. 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. 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.[28] Given the complexities of master protocols, a DMC may be particularly important for protecting the safety of participants and maintaining trial integrity, for example, by ensuring the confidentiality of information across substudies (discussed further below). Depending on the trial design, the sponsor may also 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 risks to trial integrity. For example, in an event-driven umbrella or platform trial in which multiple drugs enter the study simultaneously, 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), reporting a finding that the first drug is superior to the control could suggest that a drug remaining in the trial is also superior to the control because it would have had even fewer events of poor outcomes. Conversely, if the endpoint represents the time to an event capturing a good outcome (e.g., recovery), reporting a finding of futility for

[26] For a detailed discussion of selective safety collection, including factors to consider in pursuing this approach, see the ICH guidance for industry *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials* (December 2022).

[27] 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).

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

the first drug could suggest futility for a drug still under evaluation in the trial because it would have had even fewer events of good outcomes. Such dissemination of information could influence 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 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.[29]

In general, in master protocols evaluating multiple drugs, the DMC and study team should carefully consider data access plans and how best to plan analyses and communicate results for individual drugs without 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.F).

However, the leveraging of data from other drugs still under ongoing evaluation necessitates some degree of access to unblinded interim results. Such access 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 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 trials using a master protocol. These recommendations primarily apply to the master protocol sponsor. 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 interested parties, the potential for frequent changes, and the quantity of documentation. Because of these complexities, each master protocol should be submitted in a new IND to FDA.

[29] Sponsors of master protocol studies that are required to be registered in clinicaltrials.gov may submit a good cause extension request to extend the deadline for submitting the required clinical trial results information due to the need to preserve the scientific integrity of the study. For additional information, refer to: https://cdn.clinicaltrials.gov/documents/GCE_Criteria_final_508.pdf.

A. General Investigational New Drug Considerations

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

- The master protocol sponsor should request a pre-IND meeting to discuss the protocol and submission details.[30] The cover letter for these meeting requests should clearly state "REQUEST FOR MEETING-MASTER PROTOCOL (Meeting Type B)." Due to the complexities associated with master protocols, multiple meetings may be needed before the submission of the IND.

- Clinical investigations using a master protocol should generally be conducted under the master protocol IND only. However, in some basket trials and platform trials with basket components, submission of separate INDs for new substudies (i.e., substudy INDs) may be appropriate, particularly when the required subject matter expertise for evaluation of the proposed investigations resides in multiple review divisions. It is generally expected that such an approach will involve a single sponsor (the master protocol sponsor) of the master protocol IND and all substudy INDs. Master protocol sponsors should discuss the planned submission approach with the relevant review division(s), considering the planned patient populations, study design, and analytical approach (e.g., whether the analysis may leverage information across different substudies). Refer to section V.B for information regarding cross-referencing when submitting different substudy INDs and section V.C for information regarding updates to the master protocol or its substudies.

- The master protocol trial should be the only trial conducted under the master protocol IND (and substudy INDs, if applicable).

- 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).[31]

- 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

[30] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[31] 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.

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.

- 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.

- Although most clinical investigations using master protocols will be required to be conducted under an IND, a clinical investigation using a master protocol may be exempt[32] from this requirement in select circumstances. For example, the clinical investigation would be exempt if all the substudies of a master protocol meet the criteria for an IND exemption under 21 CFR 312.2(b)(1). However, 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.[33]

    - 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,[34] the master protocol sponsor should submit an IND before making those changes.

- The Agency may place the clinical investigation under the master protocol on full clinical hold if the deficiency(ies) identified apply to the overall protocol and, therefore, all substudies of the master protocol. The Agency may place the clinical investigation under a master protocol on partial hold if the deficiency(ies) identified do not apply to the overall protocol, but to a specific substudy or substudies conducted under the master protocol.[35]

B. IND Cross-Referencing

The following are recommendations regarding cross-referencing between the master protocol IND and other INDs:

- To facilitate FDA review of investigational drugs evaluated in a master protocol, the master protocol IND should cross-reference relevant, previously submitted information in the INDs for the individual investigational drugs, such as nonclinical study findings, drug product quality specifications, and clinical data.

- 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).

[32] 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).
[33] See 21 CFR 312.2.
[34] For example, when there is an addition of a new arm in a platform trial that does not meet exemption criteria.
[35] See 21 CFR 312.42.

- For master protocols with submission of separate substudy INDs, the master protocol sponsor should cross-reference relevant previously submitted information in the master protocol IND rather than resubmit the information to the substudy IND. Also, the master protocol IND should cross-reference information in the substudy IND. Refer to section V.C for further information on cross-referencing when there are updates to the master protocol or its substudies.

- To cross-reference information in another sponsor's IND, a signed, written statement from that sponsor authorizing such cross-reference must be provided.[36]

C. Updates to the Master Protocol or its Substudies

Given the potentially rapid pace of changes associated with master protocols, FDA recommends the following procedures for updates to the master protocol or its substudies:

- For master protocols with submission of all substudies under the master protocol IND, a potential new substudy (e.g., a new drug or a new population proposed to be evaluated under the master protocol) should be submitted to the master protocol IND as a protocol amendment. Any proposed changes to the master protocol or one of its substudies should also be submitted as protocol amendments.

- For master protocols with submission of separate substudy INDs, master protocol sponsors should follow these procedures:

    - If a new substudy is being initiated, the substudy protocol should be submitted to a new, separate substudy IND. There should also be submissions to the master protocol IND and to all other substudy INDs to notify about the new substudy and cross-reference the new substudy IND.

    - If the master protocol is amended, a protocol amendment should be submitted to the master protocol IND. There should also be submissions to all the substudy INDs to notify about the changes and cross-reference the master protocol IND.

    - If a substudy protocol is amended, a protocol amendment should be submitted to the substudy IND. There should also be submissions to the master protocol IND and to all other substudy INDs to notify about the changes and cross-reference the respective substudy IND.

- The cover letter for submissions of major changes (e.g., initiation of a new substudy, amendment of a key design element) to a master protocol IND should include the status of each substudy in the master protocol (e.g., on which substudies are open and complete, the status of enrollment, and the substudy IND number, if different from the master protocol IND). Sponsors should also consider including such information in the cover letter for other types of submissions to the master protocol IND.

[36] See 21 CFR 312.23(b).

826
827 • The master protocol sponsor should clearly mark the cover letter for protocol
828 amendments with "Protocol Amendment-MASTER PROTOCOL," and include a clean
829 and tracked changes version of the amended document as well as a separate document
830 specifying what changes are being made.
831
832 • The master protocol sponsor should submit protocol amendments that substantively affect
833 the safety, quality, or scope of the master protocol at least 30 days before initiation of the
834 changes.[37] For example, in the case of a master protocol with submission of all substudies
835 under the master protocol IND, the master protocol sponsor should submit a new
836 substudy at least 30 days before initiating the substudy to allow sufficient time for FDA
837 to review potential changes that may impact the safety of participants (e.g., use of a new
838 drug, different dosing regimen/dosage, or different patient population).
839
840 • The master protocol sponsor should notify the regulatory project manager at least 48
841 hours before submitting any protocol amendment that could substantively affect the
842 safety, quality, or scope of the master protocol.
843
844 **D. Communications and Safety Reporting**
845
846 The master protocol IND should include a well-designed communication plan to ensure timely
847 and effective communications between interested parties and to help ensure compliance with
848 legal requirements (see Figure C). FDA recommends that a communication plan be employed by
849 the master protocol sponsor to ensure the dissemination of information and advice from FDA to
850 the individual drug sponsor(s). Additionally, the master protocol sponsor should establish a
851 systematic approach that ensures the rapid communication of serious safety issues to clinical
852 investigators and FDA under IND safety reporting regulations.[38] This approach should include a
853 process for rapid implementation of protocol amendments to address serious safety issues.[39]
854 With regard to safety reporting, sponsors should be aware of the following:[40]
855

[37] Per 21 CFR 312.30(b)(2)(ii), when changes to the protocol are intended to eliminate an apparent immediate hazard to participants they may be implemented immediately provided that FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c).
[38] See 21 CFR 312.32.
[39] See 21 CFR 312.30(b)(1) and 312.30(b)(2)(ii).
[40] 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.

- All clinical investigators are required to submit safety reports to the master protocol sponsor.[41]

- 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).[42]

- 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.[43]

    - The individual drug sponsor should review each safety report, add any relevant context or additional information, and submit an initial safety report and any relevant follow-up information to their active IND(s) for the investigational drug, if required,[44,45] that references the IND safety report submitted by the master protocol sponsor.

[41] See 21 CFR 312.64(b)). Also, see 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.

[42] 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.

[43] See 21 CFR 312.32(b).

[44] See 21 CFR 312.32(c)(1).

[45] See 21 CFR 312.32(d).

875 **REFERENCES**[46]
876
877 Brown, BM and TP Hettmansperger, 2002, Kruskal-Wallis, Multiple Comparisons and Efron
878 Dice, Australian and New Zealand Journal of Statistics 44(4): 427–438.
879
880 Chandereng, T, X Wei, and R Chappell, 2020, Imbalanced Randomization in Clinical Trials.
881 Statistics Medicine, 39(16): 2185–2196.
882
883 Howard, DR, JM Brown, S Todd, and WM Gregory, 2018, Recommendations on Multiple
884 Testing Adjustment in Multi-arm Trials with a Shared Control Group, Statistical Methods in
885 Medical Research, 27(5): 1513-1530.
886
887 Jiao, F, W Tu, S Jimenez, and YF Chen, 2019, Utilizing Shared Internal Control Arms and
888 Historical Information in Small-Sized Platform Clinical Trials, Journal of Biopharmaceutical
889 Statistics, 29(5): 845-859.
890
891 Lee, KM, and J Wason, 2020, Including Non-Concurrent Control Patients in the Analysis of
892 Platform Trials: is it Worth it?, BMC Medical Research Methodology, 20: 165.
893
894 Proschan, MA and DA Follmann, 1995, Multiple Comparisons with Control in a Single
895 Experiment Versus Separate Experiments: Why Do We Feel Differently?, The American
896 Statistician, 49: 144.
897

[46] Some of the listed references also apply to the Appendix.

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 demonstration using 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 participants, k drugs, and 1 control group. For some fraction p suppose that $N \times p$ participants are assigned to control and $N \times (1-p)/k$ participants 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:

$$f(p) = \frac{k}{N(1-p)} + \frac{1}{Np}.$$

Considering p as continuous in $(0, 1)$ (even though strictly speaking the number of treatment and control participants are integers) the first derivative of $f(p)$ is

$$f'(p) = \frac{k}{N(1-p)^2} - \frac{1}{Np^2}.$$

The second derivative of $f(p)$ is

$$f''(p) \quad = \frac{2k}{N(1-p)^3} + \frac{2}{Np^3} > 0,$$

so the function $f(p)$ is convex, and thus the 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 $k > 1$. In a platform trial where drugs enter and leave and the number of drugs being evaluated changes over time, the derivation of the optimal allocation ratio is more complex and may depend on factors such as the degree to which the evaluation periods of different drugs overlap.

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 participants and there

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

are 4 drugs and 1 shared control group. Optimal allocation of 200 participants ($p = \frac{1}{3}$) to the shared control group and 100 participants to each drug group would result in 300 participants and optimal power for the comparison of a given drug to the control group. Equal allocation to all groups ($p = \frac{1}{5}$) would result in 120 participants allocated to each drug group and to the control group, resulting in only 240 participants for the comparison of a given drug to the control group.

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

Example 1: Randomization Process for 1:1 Allocation Ratio

Here is an 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 ($1:1:\ldots:1$) to one of the drugs the participant is eligible to receive.

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 participant 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 is to first randomize participants to one of the drugs or the pooled placebo arm with equal probability and then randomize participants in the pooled placebo arm to one of the drug-specific placebos with equal probability. A second alternative is to first randomize participants to drug or placebo in a $k:1$ ratio and then randomize participants 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 to increase power with greater-than-equal allocation to placebo (see Appendix: section A):

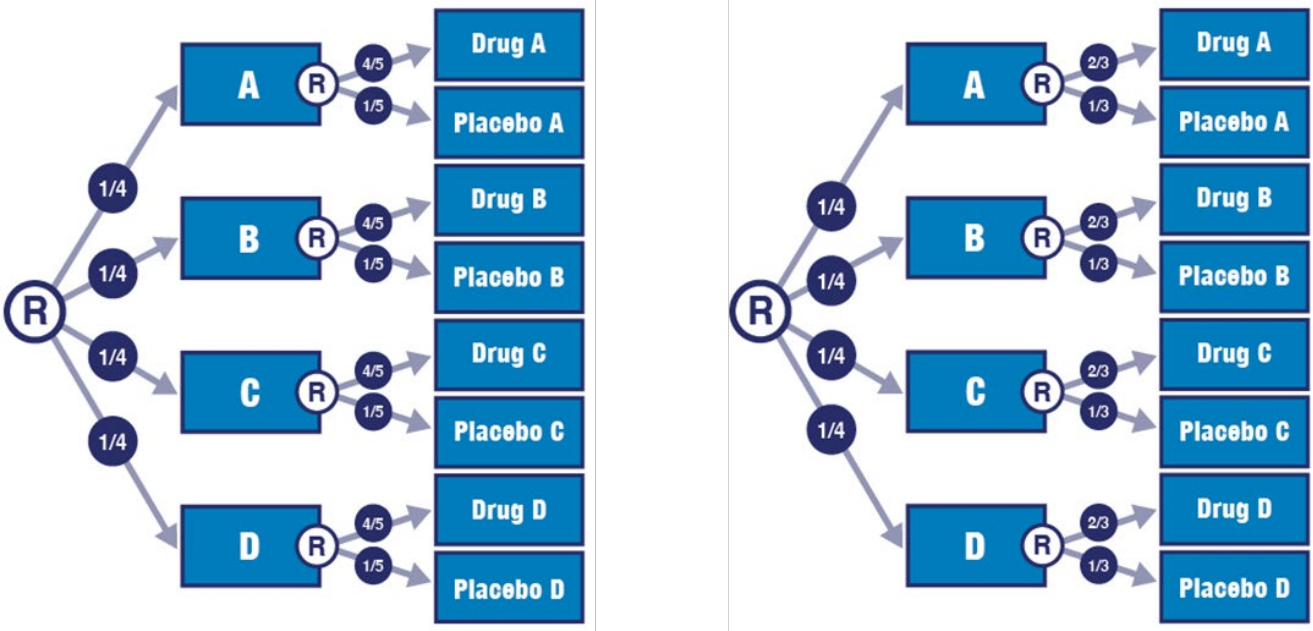
1. Randomize with equal probability ($1:1:\ldots:1$) to one of the drugs the participant is eligible to receive.

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 participant is eligible.

Illustrative Figure and Table

Figure A illustrates the two example randomization processes described above in a trial with four drugs for a participant who is eligible to receive all four drugs. Table A 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.

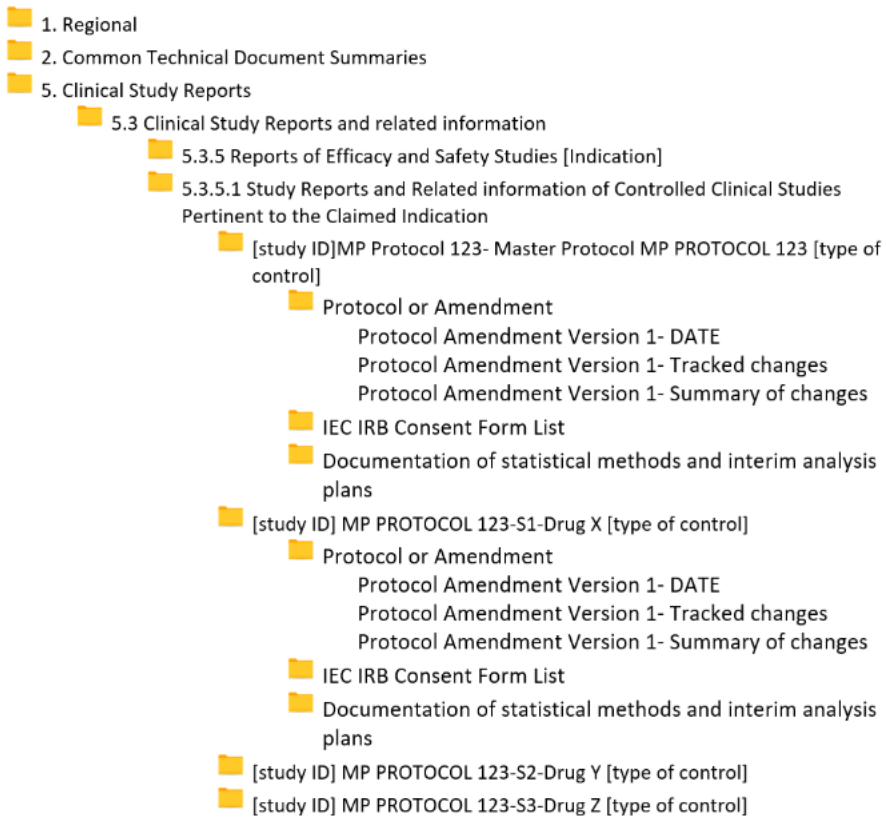
Table A: Randomization Probabilities and Ratios for Examples of Randomization Processes for a Partially-Blinded, Placebo-Controlled Study

	Example 1	Example 2
Allocation ratio for the pooled placebo arm relative to a given drug	**1:1**	$\sqrt{k}$**: 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

Figure B 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
Figure shows the eCTD display and not the folder structure for submitting the files.

D. Expected Communications Between the Master Protocol Sponsor, Individual Drug Sponsors, and FDA

Figure C depicts communication channels among the various sponsors (left) and FDA (right) in the setting of an umbrella or platform trial conducted under a master protocol to evaluate multiple drugs for a single disease.

Left: There is bidirectional communication between the individual drug sponsors and the master protocol sponsor. The master protocol sponsor communicates information regarding the master protocol, including information about the individual drugs in its substudies, to the relevant individual drug sponsor(s). In this figure, information regarding drug A in substudy A is shared with individual drug sponsor A, and information regarding drug B in substudy B is shared with individual drug sponsor B. As shown in the figure, individual drug sponsor A communicates information regarding drug A to the master protocol sponsor, and individual drug sponsor B communicates information regarding drug B to the master protocol sponsor.

Right: There is bidirectional communication between the various sponsors and FDA via their respective IND. In this case, communications regarding drug A occur between the individual

drug sponsor for drug A and FDA via the IND for drug A; communications regarding drug B occur between the individual drug sponsor for drug B and FDA via the IND for drug B; and communications regarding the master protocol, including information about the individual drugs contained in substudies A and B, occur between the master protocol sponsor and FDA via the master protocol IND.

Figure C. Expected Communication Among Interested Parties in a Master Protocol with Substudies A and B, Where the Master Protocol Sponsor is Different than the Individual Drug Sponsor