U.S. FOOD & DRUG ADMINISTRATION

Draft Guidance for Industry

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

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Disclosure

- I have no conflict of interest.

Master Protocols

- Use a single infrastructure and trial design to simultaneously investigate multiple drugs and/or disease populations within the overall trial structure.
- Each substudy within the master protocol has specific objectives, scientific rationale and justification of the number of patients that would be require to address the proposed objectives

Draft Guidance for Industry: Master Protocols

- Draft guidance published on October 2018
- Public comment period closed November 30, 2018
- FDA is currently reviewing and considering the comments that it has received and plans to issue the final guidance as soon as possible.

Reason for the Guidance

- Increased interest among the academic community and pharmaceutical sponsors
- Guidance to facilitate development of well-designed protocols
- Provides advice on the information that Sponsors should submit to FDA
- Advice on how Sponsors should interact with FDA to facilitate efficient review

Reason for the Guidance

- Patient Safety
  - Complexity and rapid accrual
  - Pose increased risk to patients due to failure to quickly identify and communicate adverse events
  - Potential exposure of new patients to investigational agents with limited or no activity

- Importance of safety monitoring
  - Communication of serious safety issues to investigators
  - Implementation of protocol amendment to address serious safety issues.

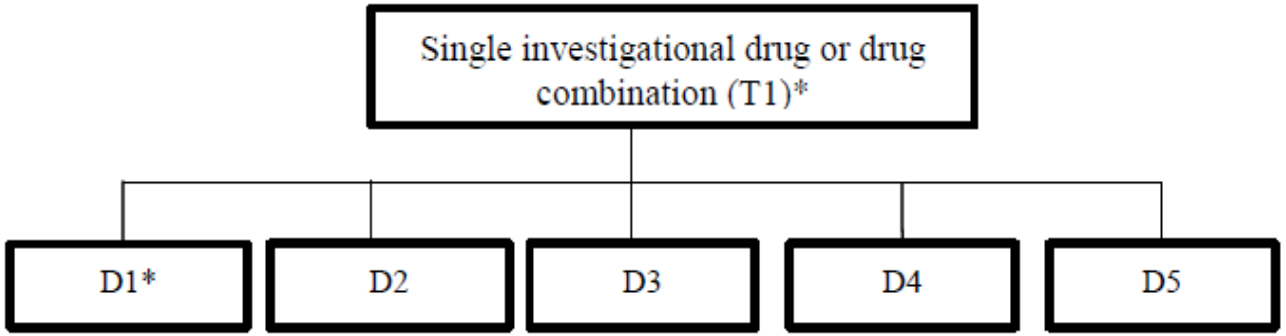
Opportunities and Challenges

- Flexibility and efficiency in drug development

- Challenges
  - Attribution of Adverse Events to one or more investigational drugs
  - Assessing safety profile: multiple drugs across multiple protocols and INDs
  - Overinterpretation of interim findings - potential delays in drug development

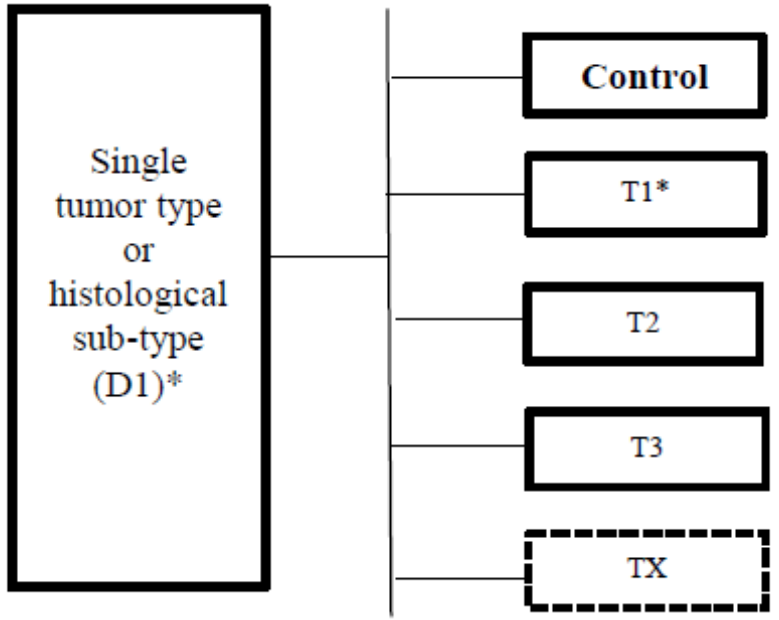
Types of Master Protocol

Basket Trial Design



T=investigational drug; D= Protocol defined subpopulation in multiple disease subtypes

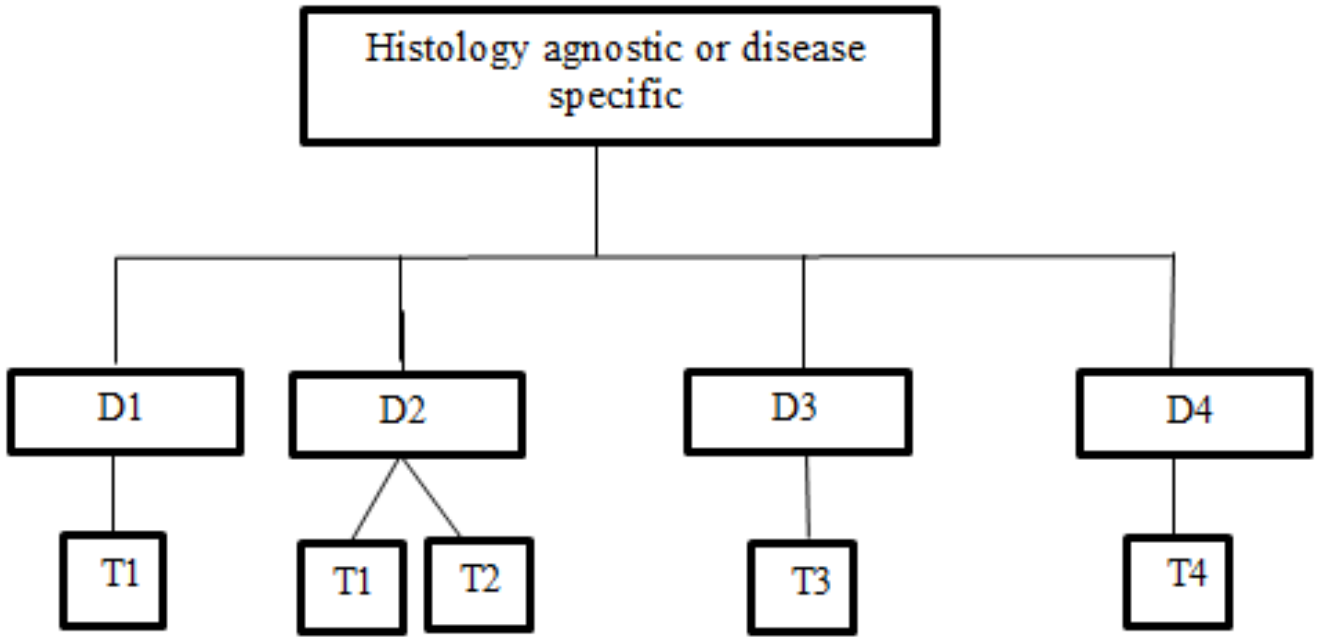
Umbrella Trial Design



T=investigational drug; D= Protocol defined subpopulation in single disease subtypes TX= future treatment arm

Types of Master Protocol

Complex Trial Designs



D= Protocol defined subpopulation in multiple disease subtypes T=investigational drug

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Master Protocol Design Considerations

- Dosing: Recommend that RP2D for each individual drugs established
- Unique aspects associated with Master Protocol design
  - Common Control Arm
  - Novel Combinations
  - Adding and Stopping Treatment Arms
- Independent Data Monitoring
- Biomarker Development
- Statistical Considerations

Use of a Single Common Control Arm

- Preferred to improve efficiency (umbrella trials)
- Recommend current SOC (US medical practice)
- Changes in SOC: suspend enrollment (revise protocol, SAP, consent form)
- Analysis between test drug and control

Novel Combination of Two or more Investigational Products

- Provide strong scientific rationale for use
- For each product: FIH, RP2D
- Contribution of each investigational drug to the treatment effect

Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination

Adding and Stopping Treatment Arms

- Prior to initiating the trial: detailed SAP
- Describe conditions to add new experimental arm
- Sample size re-estimation
- Experimental arm closure: futility rules

Refer to: Draft guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics

Studies with Drugs Targeting Multiple Biomarkers

- Definition for maker positivity prior to initiation for each biomarker
- Pre-specified plan for allocations of patients: eligible for ≥ 1 substudy
- Sample size, patient allocation: prognostic implications

Independent Oversight

Potential marketing application

- IDMC charter – monitor for efficacy results
- Independent radiologic review committee

Safety

- ISAC

Biomarker Development

- IVD assays must be analytically validated for performance
- Procedures for sample acquisition, handling, testing and analysis plans early in development
- Justification for use of each biomarker
- If IVD used for patient selection
- contact FDA early to obtain risk assessment and guidance
- Assess requirement for IDE at 21 CFR Part 812

Statistical Considerations

- Non-Randomized, activity-estimating design
  - Primary endpoint is ORR: sample size justification and stopping rules of futility. e.g. Simon 2-stage design.
  - Limit exposure of large number of patients to ineffective drug.
  - If results warrant seeking approval: SAP ensure that data collected is of adequate quality to support approval
  - Efficacy: blinded independent radiographic review
- Randomized activity estimating protocols
  - Umbrella design: use of common control arm recommended
  - Comparative analyses between test drug and control
  - Avoid formal comparison between experimental arms

Statistical Considerations

- Protocols employing adaptive design strategies
  - Use Bayesian statistical method or other methods
  - SAP should include details on implementation of Bayesian methods: details futility analysis and the criteria for when and how to modify the sample size

- Protocols with biomarker defined sub-groups
  - When patient assignment to treatment arm is based on specific biomarker, SAP should pre-specify how patients with multiple markers will be assigned in to one of the substudies

Safety Considerations

- Ensure proper monitoring
- Ensure rapid communication of serious safety issues to investigators and regulatory authorities
- Periodic safety reports: more frequently than annually
- Independent safety monitoring (ISAC or IDMC)

Question

Will the Guidance be mandatory once it is finalized?

No. In general, FDA's guidance documents do not establish legally enforceable responsibilities. This guidance describes the Agency's current thinking on the use of master protocol design trials and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

Question

Master Protocol Guidance WG

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Draft Guidance for Industry

Use of Expansion Cohorts in First-In-Human Clinical Trials to Expedite Development of Cancer Drugs and Biologics

August 2018

Expansion Cohorts in FIH Clinical Trials

Guidance provides FDA's current thinking regarding:

- Characteristics of products that are best suited for consideration for development under a multiple expansion cohort study
- Information to include in IND submissions to justify the design of individual expansion cohorts
- When to interact with FDA on planning and conduct of multiple expansion cohort studies, and
- Safeguards to protect subjects enrolled in FIH expansion cohort studies

Additional References

- Guidance for industry Codevelopment of Two or More New Investigational Drugs for Use in Combination https://www.fda.gov/regulatory-information/search-fda-guidance-documents/codevelopment-two-or-more-new-investigational-drugs-use-combination
- Draft guidances for industry Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products
- Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. When final, these guidances will represent the FDA's current thinking on these topics. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry
- ICH guidance for industry E6(R1) and (R2) Guideline for Good Clinical Practice ICH.
- Guidance for clinical trial sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees
- Guidance for sponsors, clinical investigators, IRBs, and FDA staff FDA Decisions for Investigational Device Exemption Clinical Investigations https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-decisions-investigational-device-exemption-clinical-investigations
- Guidance for IRBs, clinical investigators, and sponsors IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE Is Needed. https://www.fda.gov/media/85294/download
- Draft guidance for industry, FDA staff, sponsors, and IRBs Investigational IVDs Used in Clinical Investigations of Therapeutic Products. When final, this guidance will represent FDA's current thinking on this topic. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-ivds-used-clinical-investigations-therapeutic-products
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Additional References

- Draft guidance for industry Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination. When final, this guidance will represent the FDA's current thinking on this topic. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-vitro-diagnostics-oncology-trials-streamlined-submission-process-study-risk

- ICH guidance for industry E9 Statistical Principles for Clinical Trials and the guidance for clinical trial sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees.

- Draft guidance for industry Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease. When final, this guidance will represent FDA's current thinking on this topic. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-targeted-therapies-low-frequency-molecular-subsets-disease

- Guidance for industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring

- Guidance for clinical investigators, sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection. https://www.fda.gov/media/72267/download

- Guidance for industry Using a Centralized IRB Review Process in Multicenter Clinical Trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/using-centralized-irb-review-process-multicenter-clinical-trials

- Guidance for industry and review staff Best Practices for Communication Between IND Sponsors and FDA During Drug Development. https://www.fda.gov/media/94850/download

- Draft guidances for industry Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. When final, this guidance will represent the FDA's current thinking on this topic. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry