



Master Protocol Design: Advantages and Challenges in Vaccine Clinical Trials

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Overview



Introduction



Master protocol structure



Advantages



Challenges and mitigation



Conclusion

□ Introduction

A Master Protocol:

- Is defined by FDA** *“as a protocol designed with multiple substudies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure.”*
- Can accelerate drug development by optimizing the information obtained and leveraging infrastructure to increase trial efficiency.

** From Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry (March 2022).



❑ Conventional vs. Master Protocol

Conventional Protocol

Molecule X
Protocol XXXXX
Date

Title Page
Unifying title placed here

Cohort A (+/- control) (*combination or disease*)
Cohort B (+/- control) (*combination or disease*)

Conventional Protocol- Substudy Appendices

Molecule X
Protocol XXXXX
Date

Title Page
Unifying title placed here

Appendix A: Sub-study A (+/- control)
(*drug combination or disease*)
Appendix B: Sub-study B (+/- control)
(*drug combination or disease*)

Master Protocol

Molecule X
Protocol XXXXX Master Protocol
Date

Title Page
Unifying title placed here

Molecule X
Protocol XXXXX Substudy A (*drug combination or disease*)
Date

Title Page
Substudy A specific title

Protocol document and study operational complexity

❑ Master Protocol Structure

Protocol Infrastructure Setup

- One Protocol, One Case Report Form (CRF), and One database
- Individual Statistical Analysis Plan (SAP) per substudy

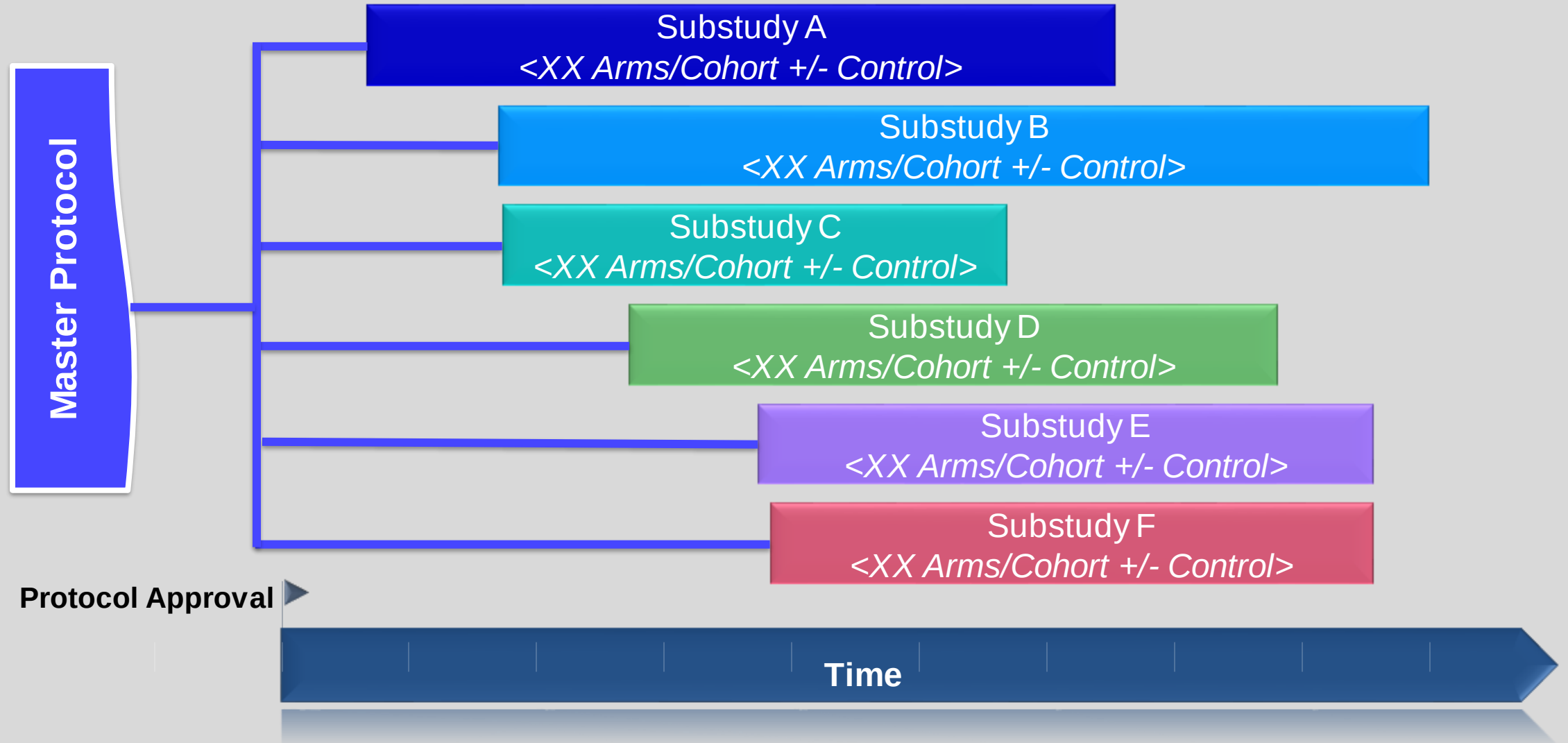
Substudy enrollment and participant identification

- Substudy Selection - identified on CRF
- Enrollment - different start date/time and priorities for each substudy
- Participants can enroll in more than one substudy under the master protocol

Protocol amendments and CRF updates

- Frequent updates
- Updates may or may not apply to all substudies

❑ Master Protocol: An Example



□ Operational Advantages

More organized approach rather than separate protocols

Reduces the startup time

Dynamically adaptable as data emerges

Common framework for multiple substudies

Analyze data simultaneously for multiple research questions

Identify the best combination of treatments faster

❏ Other Advantages

More resources well-versed with the protocol - flexibility to support each other

Updates can be consistently applied

Experience/learning can be harnessed

Study components can be cross-referenced

Advantageous in pooling for integrated analysis

❑ Operational Challenges

Challenges

- Trial infrastructure for these complex trials
- Constantly evolving

Mitigation

- ✓ Adaptable and scalable systems that support clinical execution of study:
 - Sample tracking
 - Site management
 - Randomization code generation
 - Identifying the substudy correctly
- ✓ Well-trained and experienced team members
- ✓ High degree of proactive planning, coordination

❑ Juggling Database Updates

Challenges

Mitigation

➤ Recurrent database updates to handle protocol amendments for new endpoints and/or substudies

✓ Timing the database updates for multiple substudies; combining changes, if possible

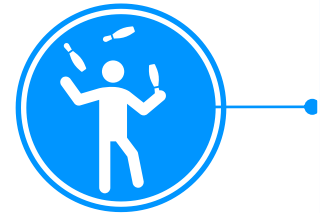
➤ Frequent data snapshots for deliverables across substudies

✓ Combine snapshots for deliverables, when feasible

➤ Overlapping timelines for substudies

✓ Prioritize and stagger timelines for activities:

- Database update for substudy X vs.
- Data snapshot for substudy Y



❑ Data Cleaning and Reconciliation

Challenges

Mitigation

➤ Possibility of participants enrolling more than once in same substudy

✓ Strict edit checks and frequent data reviews

➤ Crossover enrollment was allowed

✓ For crossover participants:

- Participant information, such as Demographics, should align between substudies

➤ Data tracking for participants crossed over between substudies

- Ensuring disposition entered is reconciled across substudies

❑ Managing Resources

Challenges

Mitigation

- Overlapping timelines caused a burden, especially for team members working across substudies

- ✓ Prioritization based on reporting event

- Unblinding of resources done on substudy basis; a resource may be blinded for one substudy and unblinded for another
- Risk of accidentally unblinding team members or sharing sensitive information

- ✓ Clear identification and documentation of blinded and unblinded team members for each substudy
- ✓ Exercising caution in communication
- ✓ Creating areas with restricted access for unblinded members

❏ Documentation

Challenges

- Identical set of documents required for each substudy in Trial Master File (TMF)
- Locating a substudy-specific document in TMF under the master protocol

Mitigation

- ✓ Consistent file naming convention (study/substudy information) for clear identification
- ✓ Regular TMF reports run to verify compliance



□ Submission

Challenges

- Multiple substudies from same master protocol included in a submission

Mitigation

- ✓ Based on FDA guidance** for electronic Common Technical Document (eCTD),
 - Section 5.2: Master protocol title along with the list of all substudies
 - Section 5.3.5: Separate folder for each substudy within the same submission
- ✓ Ensure documents for substudies such as DRGs, aCRF are:
 - Coherent
 - Uniquely identified

** From Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry (March 2022).

❑ Unblinded External Files

Challenges

- 
- Unblinded files may include sensitive data such as serology results, randomization files and protocol deviation files
 - May have more than one substudy included if the transfer is scheduled on the same day
 - So, each external file needs to be subset for the specific substudy

Mitigation

- ✓ A designated individual was unblinded for all substudies in the master protocol to:
 - Prevent accidental unblinding
 - Provide only substudy-specific information

❑ Conclusion

- Master protocols can be highly complex, require extra planning, statistical excellence, collaboration, and infrastructure. But they are successful in terms of increasing efficiency, reducing cycle time for the trial, and have a potential impact on improving patient outcomes.



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Questions?

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Thank You

