

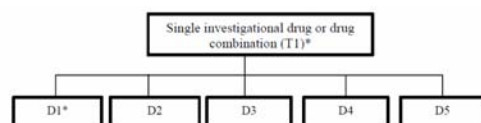
Implement SDTM and ADaM Data Standards for Trials Designed by Master Protocol

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Introduction of Master Protocol

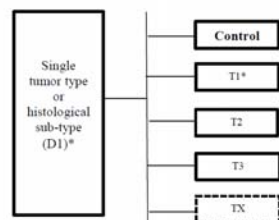
In September 2018, FDA issued draft guidance on master protocols for trial designs that test multiple drugs and/or multiple cancer subpopulations in parallel under a single protocol.

❖ A master protocol with Basket Trial Design



* T = investigational drug; D = protocol defined subpopulation in multiple disease subtypes.

❖ A master protocol with Umbrella Trial Design



* T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border depicts future treatment arm.

❖ A master protocol that incorporates design features common to both basket and umbrella design

Anticipated Changes Brought by Master Protocol

- One protocol will replace multiple protocols to achieve increased flexibility and efficiency
- The conduct and analysis of the trials may be more dynamic and complex
 - multiple investigational products, multiple types of cancer
 - many protocol amendments
 - more sites
 - adding and stopping treatment arms

Success of Master Protocol Design Requires



Considerations and Decisions on SDTM / ADaM Planning

1. One study or multiple studies

- One set of SDTM and ADaM for each sub-study is needed to support the sub-study CSR
- Consistency must be built in every aspect among sub-studies as much as possible, from the study start-up
- Plan the timeline correctly
 - Analysis will be done after the completion of each sub-study, unless unblinding to the shared control arm needs to be delayed.
- Plan for ADaM data integration of sub-studies, as complete safety profile of a product may not come from individual sub-studies

2. Using single common control arm in umbrella design

- A control arm will be shared by multiple sub-studies. Ensure the SDTM/ADaM handling of the control arm is consistent across sub-studies.
- Changes in SOC can occur during the conduct. Unknown impact on implementing SDTM/ADaM standards.

3. Data quality – prevent conformance issues from start

- Massive operation (across diseases and investigational drugs) tend to increase the chance of data issues
- Early termination of treatment arms in adaptive design could result in data that's not fully cleaned
- Build database with effective mechanism for data quality

4. Challenges to SDTM

- Trial design domain: build the domains including all planned arms, amend after protocol amendments, eligibility criteria changes, and up-version of data dictionary
- ARM/ACTARM potential issue: new variable added to SDTMIG 3.3 to explain NULL values

5. USUBJID in SDTM and ADaM

- Subjects may be enrolled in more than one sub-study. It is important to use consistent unique subject ID for the subject across sub-studies

6. Biomarker data

- Subjects may be assigned to sub-studies and treatment arms based on presence of a biomarker of interest. Subjects with more than one biomarker of interest can cause challenges to the trial conduct, and SDTM/ADaM.

7. Adjudicated data

- Adjudicated data are important in Oncology trials however there are no standard implementation about them.
- It is important to use consistent approach to represent the data in SDTM and ADaM across sub-studies and data type, and document the approach in the cSDRG and ADRG.

8. Be submission-ready

- In nonrandomized, activity-estimating design, positive preliminary results from a sub-study or sub-studies could lead to protocol amendment and regulatory submission
- cSDRG and ADRG should contain a brief summary of the master protocol design and the Statistical Analysis Plan to justify/explain the SDTM/ADaM design features that were chosen by the sponsor. Unresolved data conformance issues related to the protocol design should be clearly explained.

Conclusions

The FDA guidance doesn't predict all potential challenges associated with the master protocol design. The CDISC standards have not been tested in these innovative designs. The sponsors should have active communication with the agency on the issues they encountered, and seek input from the FDA and the CDISC group before making big implementation decisions.

The master protocol design will provide good opportunities for sponsors to build and test their data standards. It is recommended that the sponsors implement SDTM/ADaM standard for representation of clinical trial data throughout the whole duration of clinical development.