Master Protocols: What Can and Can't Be Represented in Trial Design

Presented by

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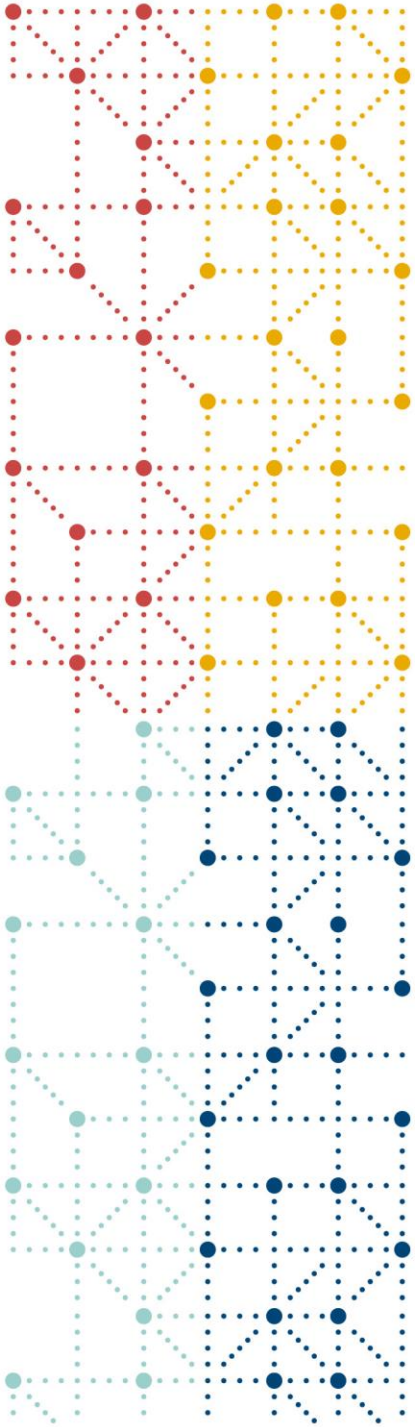
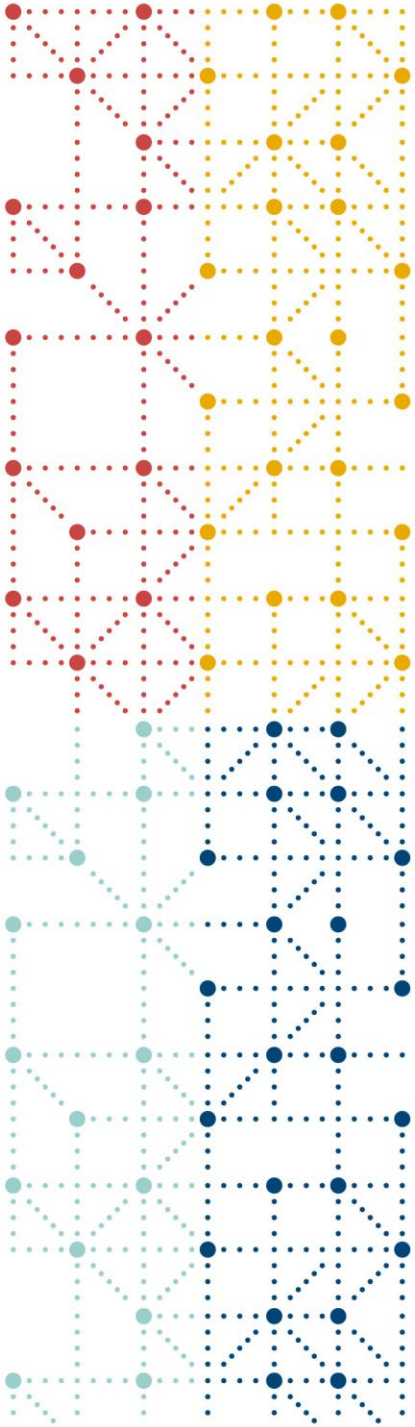
December 5, 2019



Agenda

1. Introduction
2. Trial Sets
3. State Machines
4. Conclusions



Introduction

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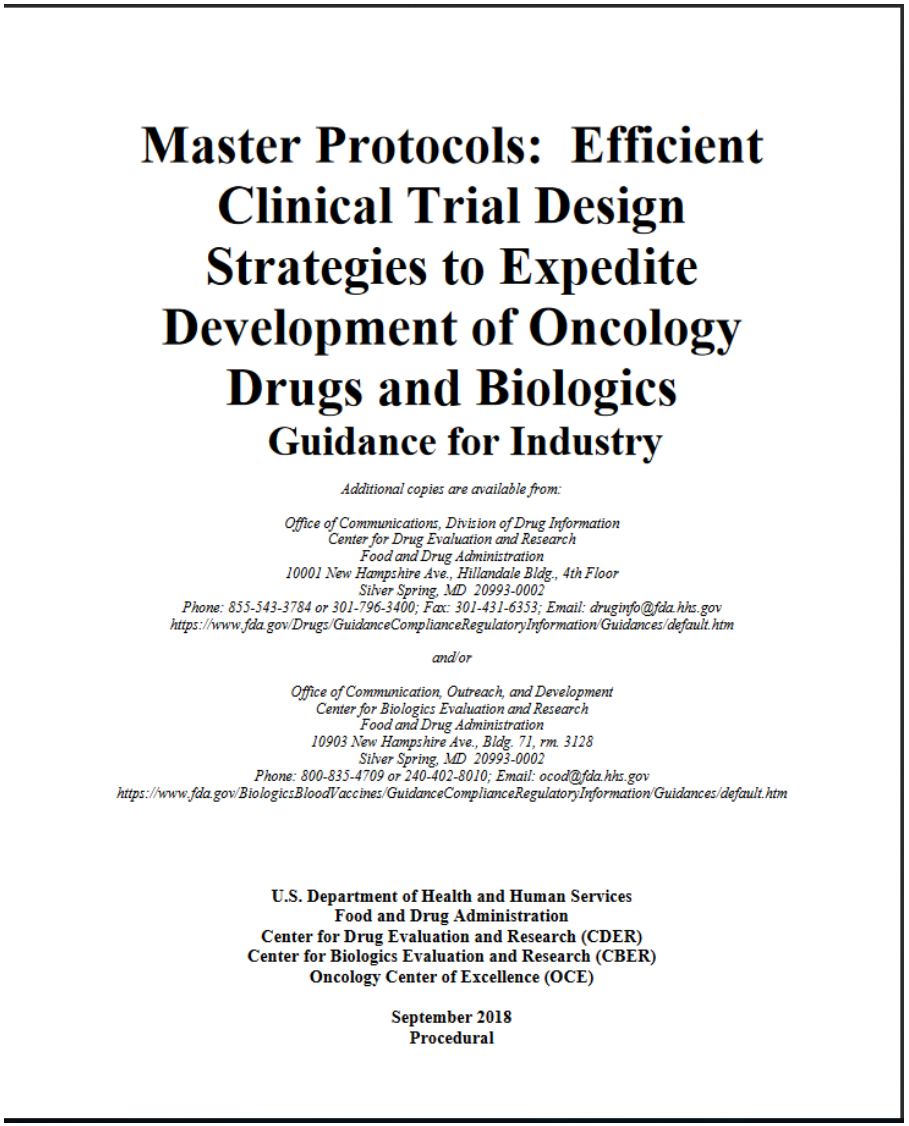


Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

Additional copies are available from:

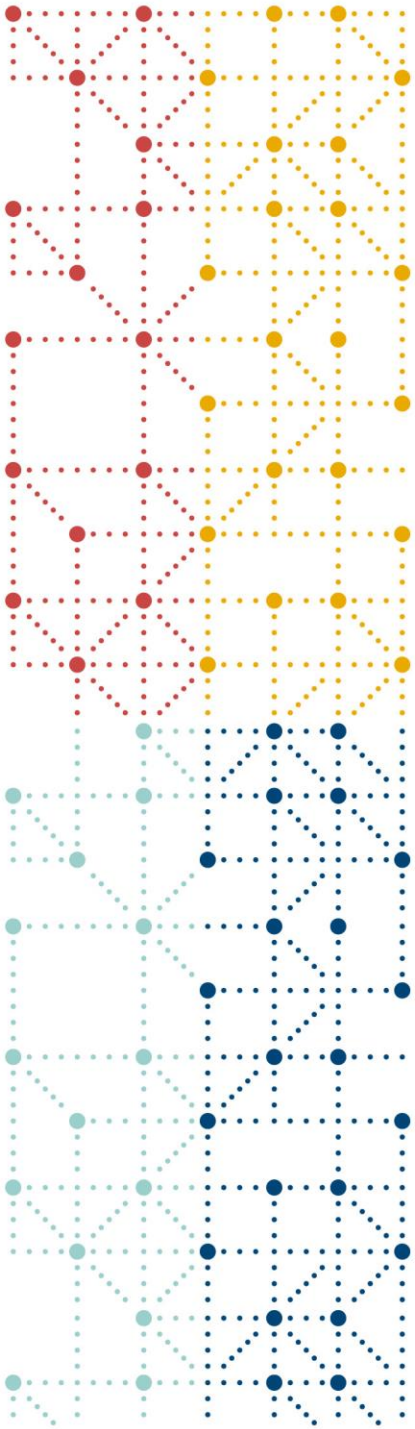
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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)
Oncology Center of Excellence (OCE)

September 2018
Procedural



Trial Sets

Trial Sets

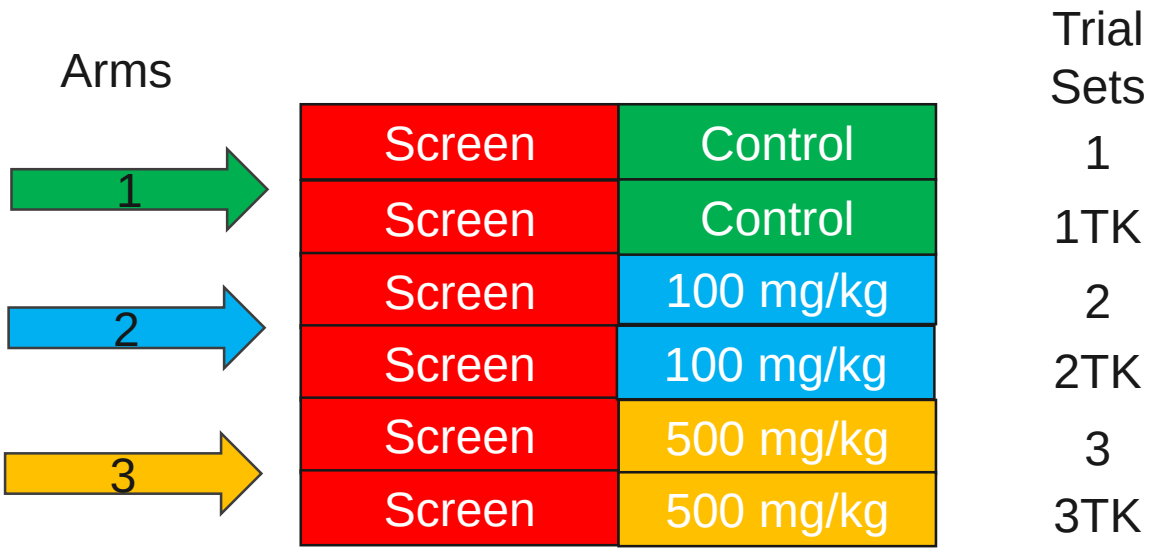
- Developed for non-clinical studies
- From the SDTM: “Trial Sets allows the submission of detailed information about planned groups of subjects that results as a combination of experimental factors of interest for a study (including experimental parameters, inherent characteristics, and sponsor-defined attributes)”
- An example from the SENDIG
- An human clinical trials example from a recent webinar
- Using trial sets for a basket trial

- A recent webinar on Trial Sets for Human Clinical Trials is available to CDISC members: https://www.cdisc.org/events/webinar/members-only-mini-training-send-trial-sets-human-clinical-trials

SENDIG Trial Sets Example

- In non-clinical trials using small animals, taking blood samples for PK can adversely affect animals.
- Studies are designed to separate sampling effects from treatment effects.
- Within each arm, animals are divided into a toxicokinetic (TK) group and a non-TK group.
- In the following example, there are 3 treatment arms, but 6 trial sets.

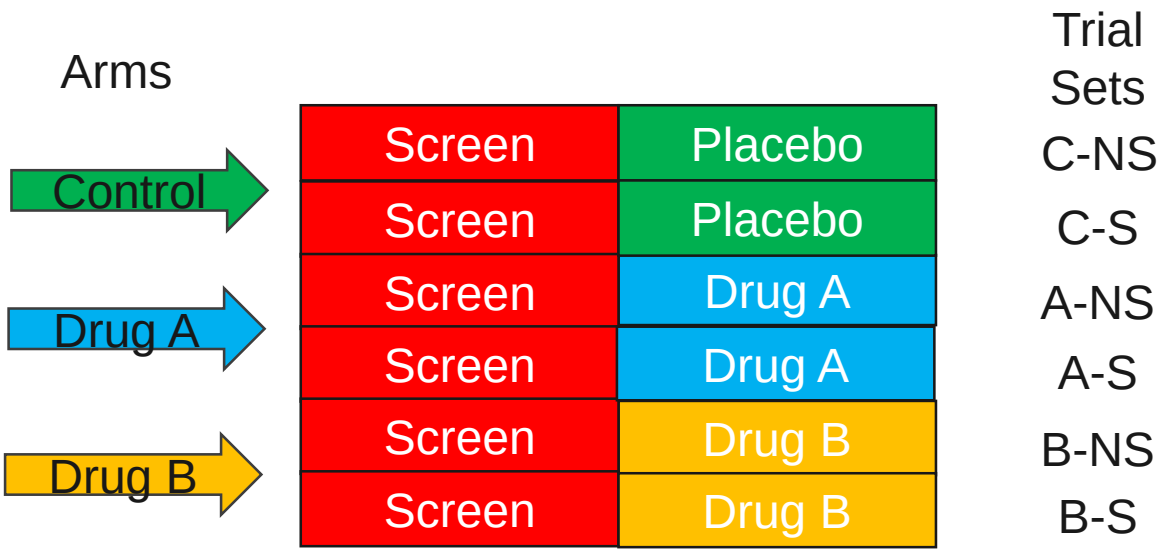
SEND TX Example 2:
6 Trial Sets Based on TA/Non-TK



Human Clinical Trial Sets Example

- This hypothetical study was designed to separate the effects of smoking status from treatment effects.
- Within each arm, there are groups of smokers and non-smokers.
- There are three treatment arms, but six trial sets.

Smoker/Non-Smoker Study

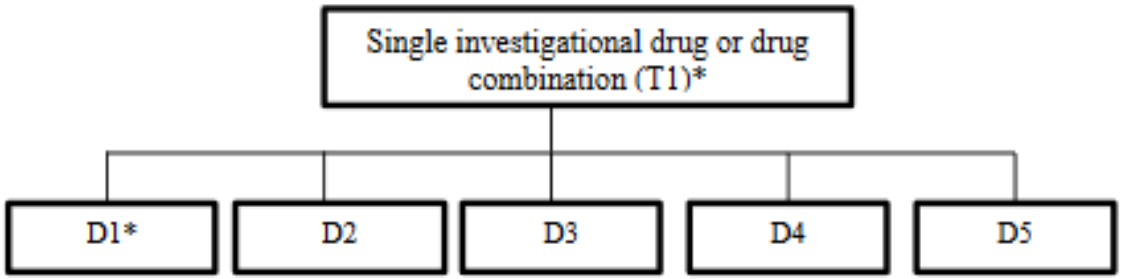


Wood, Fred, "The Standard for Exchange of Nonclinical Data (SEND): History, Basics, and Comparisons with Clinical Data", PharmaSUG 2016

Basket Trial Example

- This figure is taken from the FDA guidance.
- There is just one treatment arm, but there are five disease subtypes.
- The five disease subtypes can be represented as Trial Sets

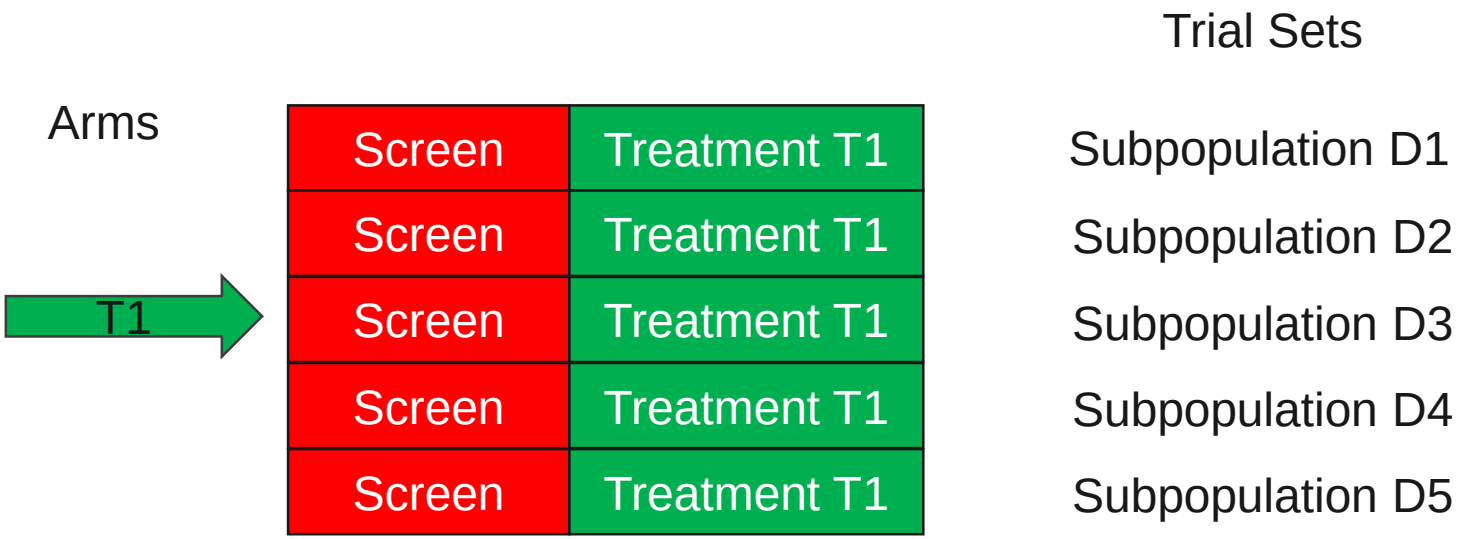
Figure 1: Schematic Representation of a Master Protocol With *Basket Trial* Design



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

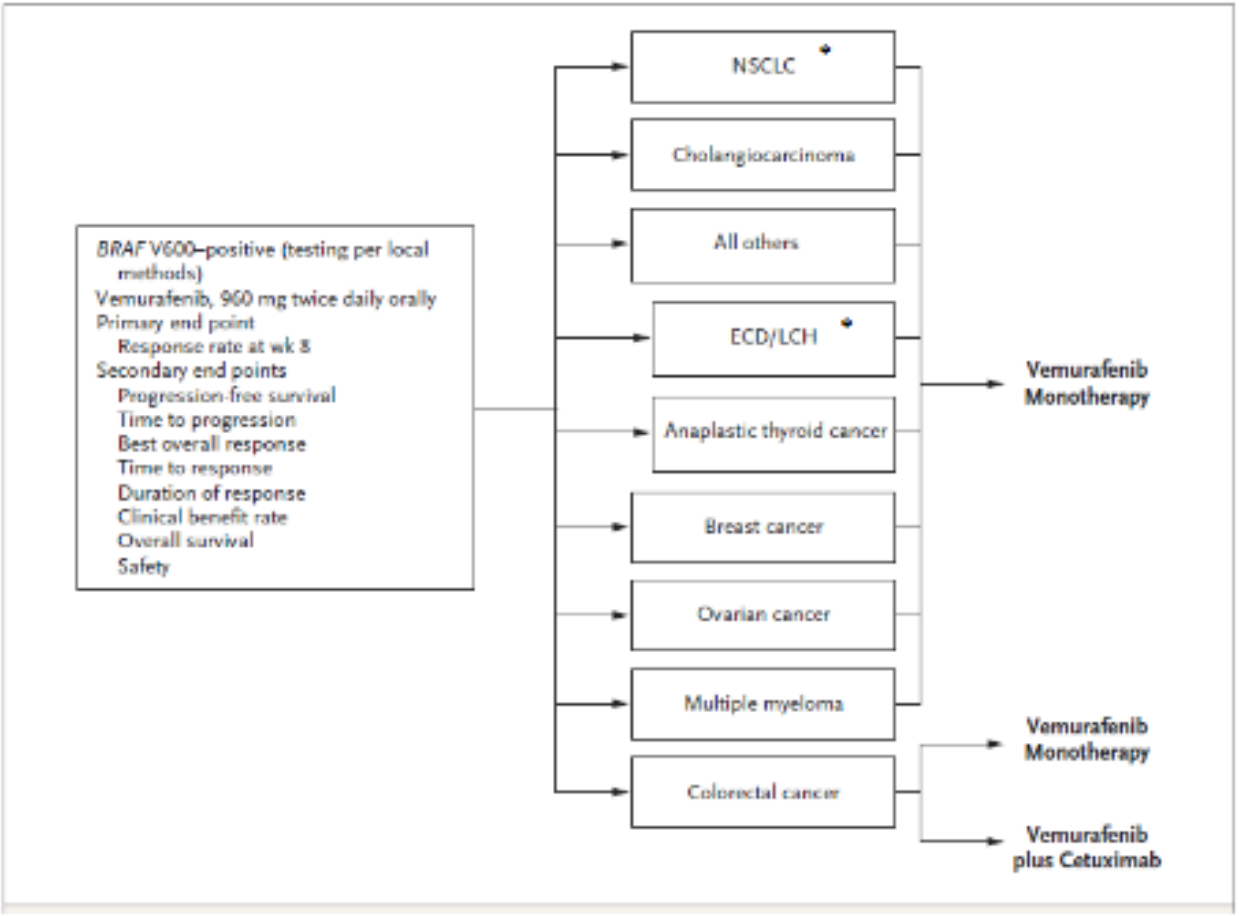
Diagram from the FDA Guidance, "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biolotics"

Trial Sets for a Basket Study



Another Basket Trial Example

Figure A: Vemurafenib in Nonmelanoma Cancers Harboring BRAF V600 Mutations[1]



*NSCLC = Non-small cell lung cancer; ECD = Erdheim-Chester disease; LCH = Langerhans cell histiocytosis.

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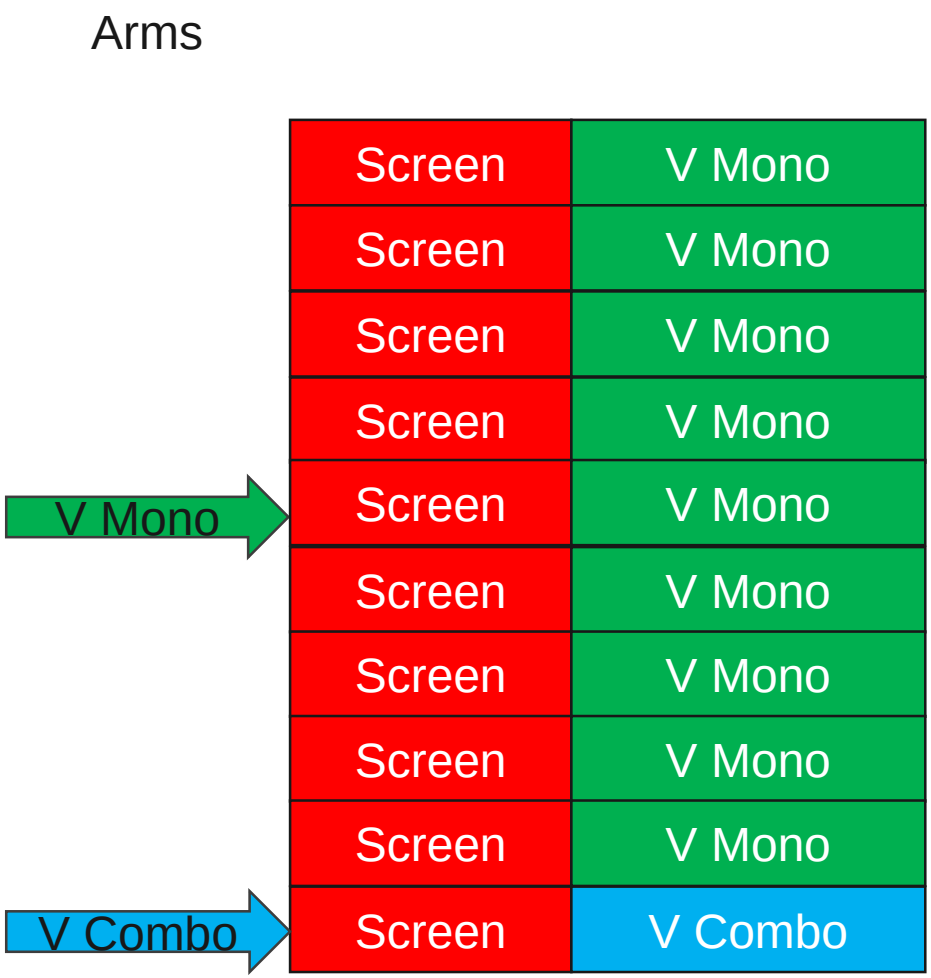
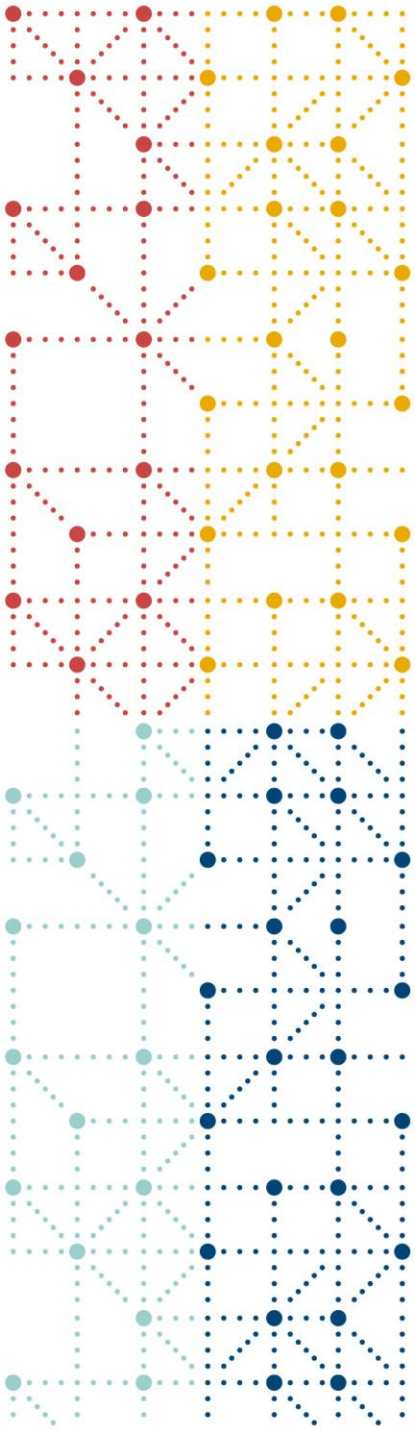
Diagram from the FDA Guidance, "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biolotics"

Trial Sets for Second Basket Study



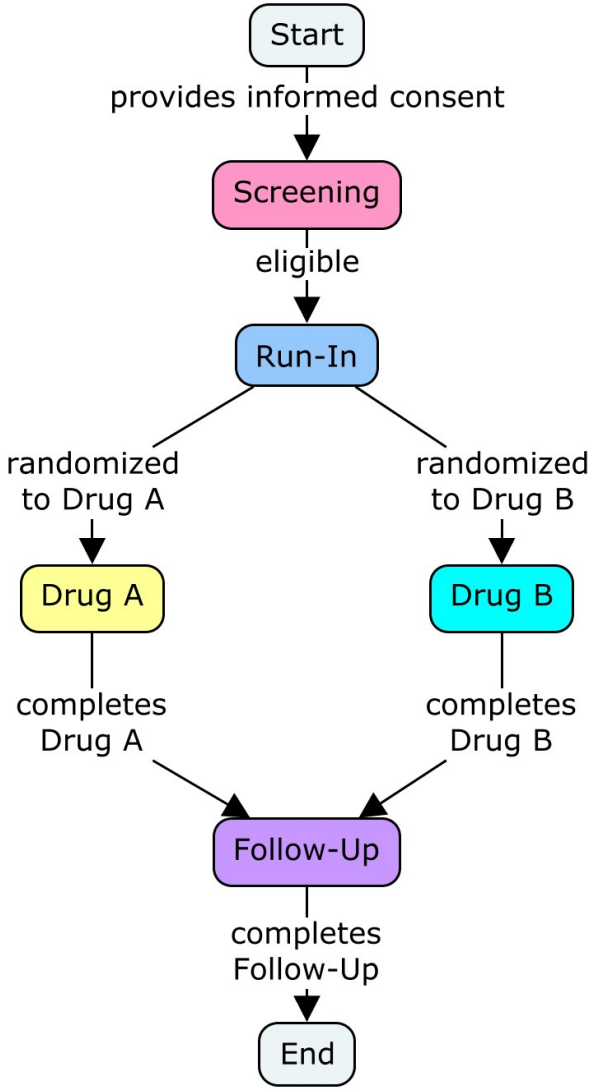


State Machines

State Machines

- A state machine is a set of “states” with rules for moving between states.
- The Trial Elements dataset describes the states (elements) in which a trial subject can be.
- The Trial Arms dataset describes some of the rules for moving from state to state – but only the planned transitions, the transitions when things are going according to plan.

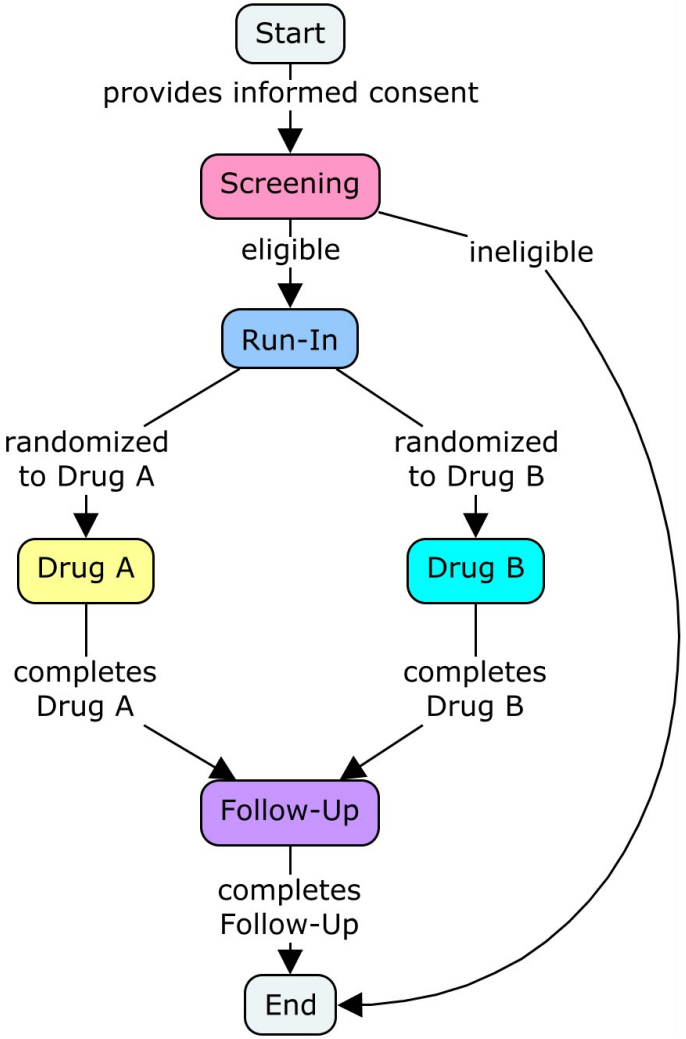
Trial Design Portion of State Machine



TA Dataset
One arm, some variables omitted

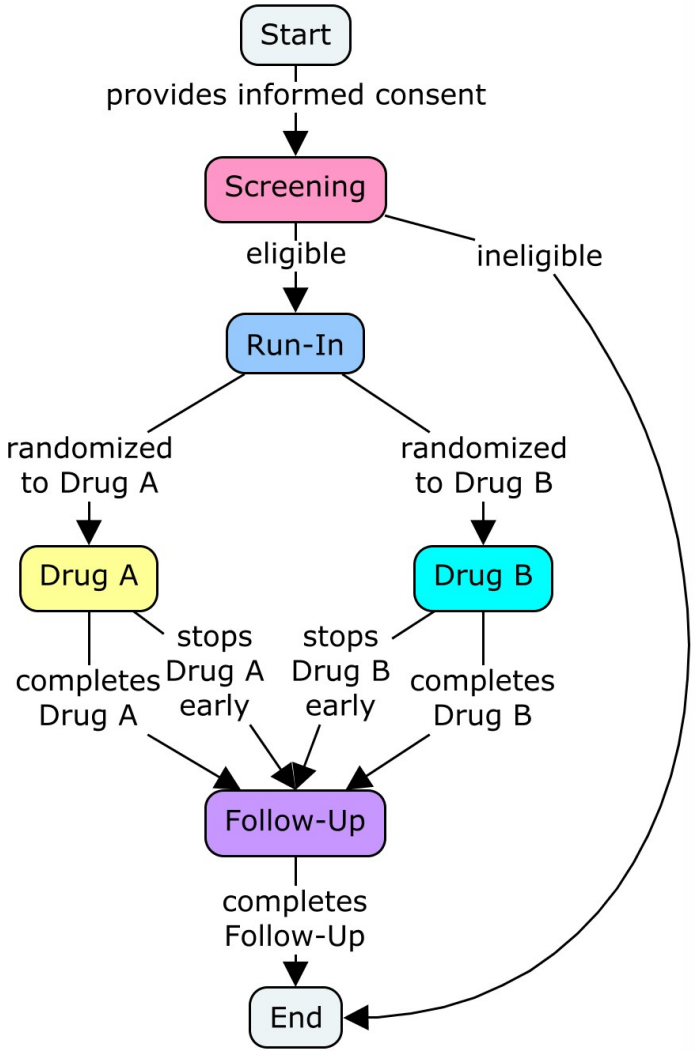
ARMCD	TAETORD	ELEMENT	TATRANS	TATRANS
A	1	SCREEN		
A	2	RUNIN		
A	3	DRUG A	Randomized to A	
A	4	FU		

Adding Transition for Ineligible Subjects

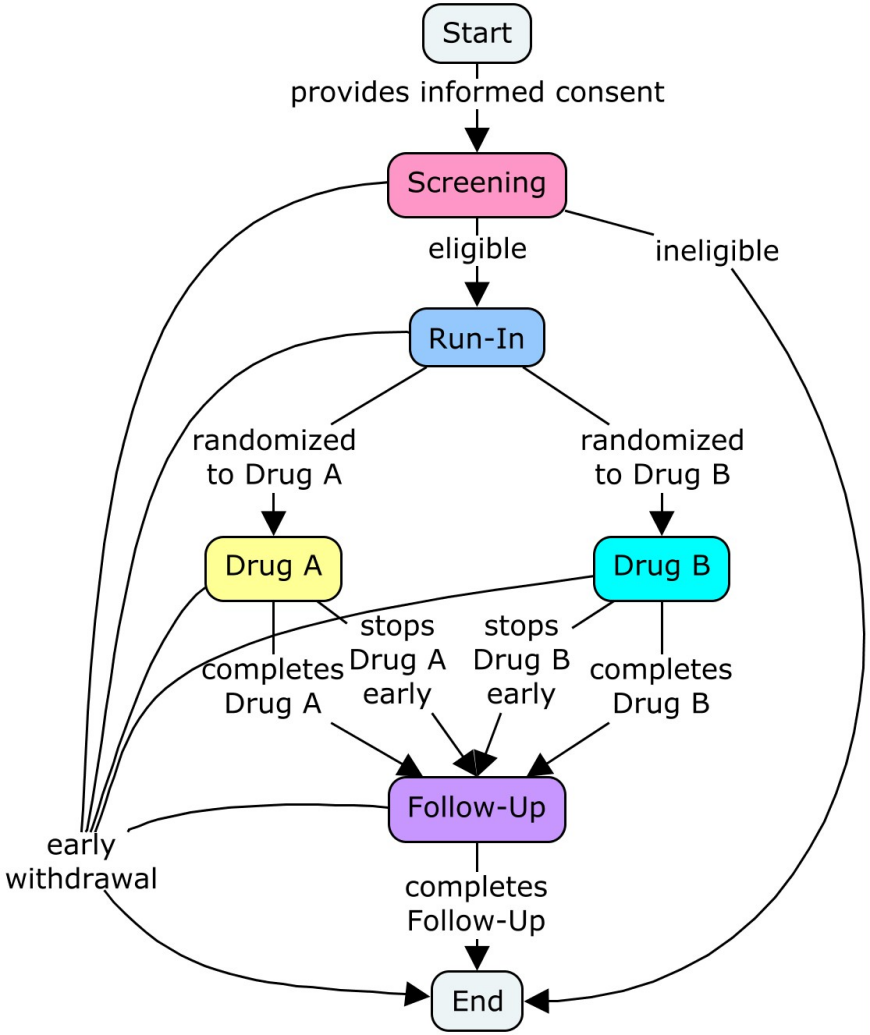


Adding Transition for Incomplete Dosing

Subjects who stop drug early still go to Follow-up



Adding Transitions for Early Withdrawals



TA Dataset with additional transition rules One arm, some variables omitted

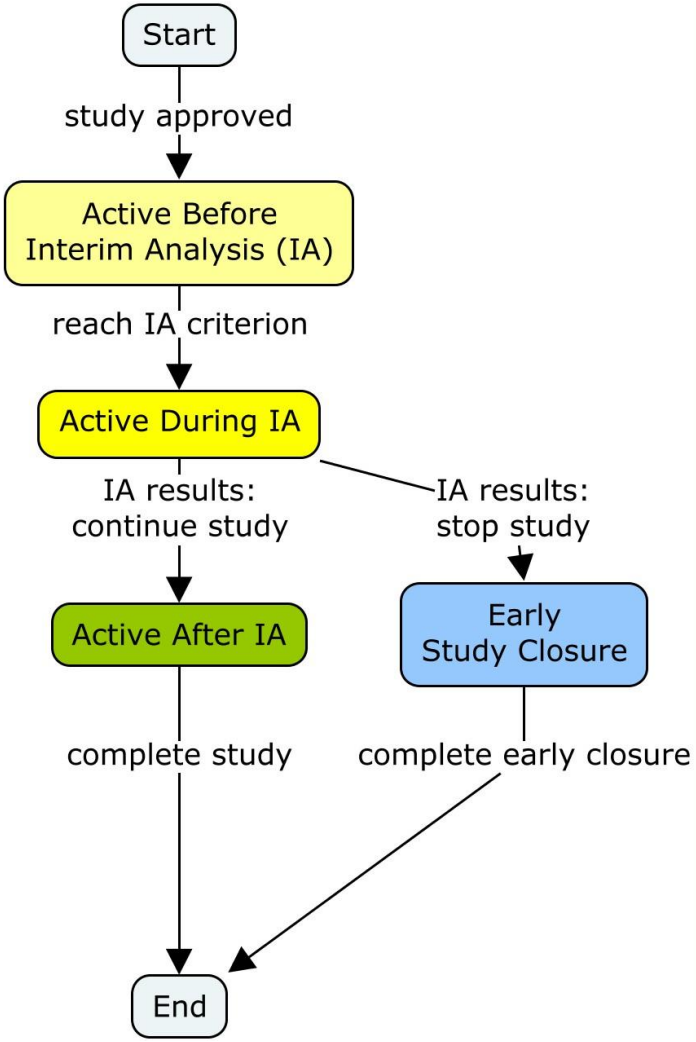
Note! This representation of additional transition rules is not necessarily supported by the SDTMIG.

ARMCD	TAETORD	ELEMENT	TABRANCH	TATRANS
A	1	SCREEN	Informed Consent	If ineligible or early withdrawal, exit trial
A	2	RUNIN	Eligible	If early withdrawal, exit trial
A	3	DRUG A	Randomized to A	If early withdrawal, exit trial
A	4	FU	Received Drug A	If early withdrawal, exit trial

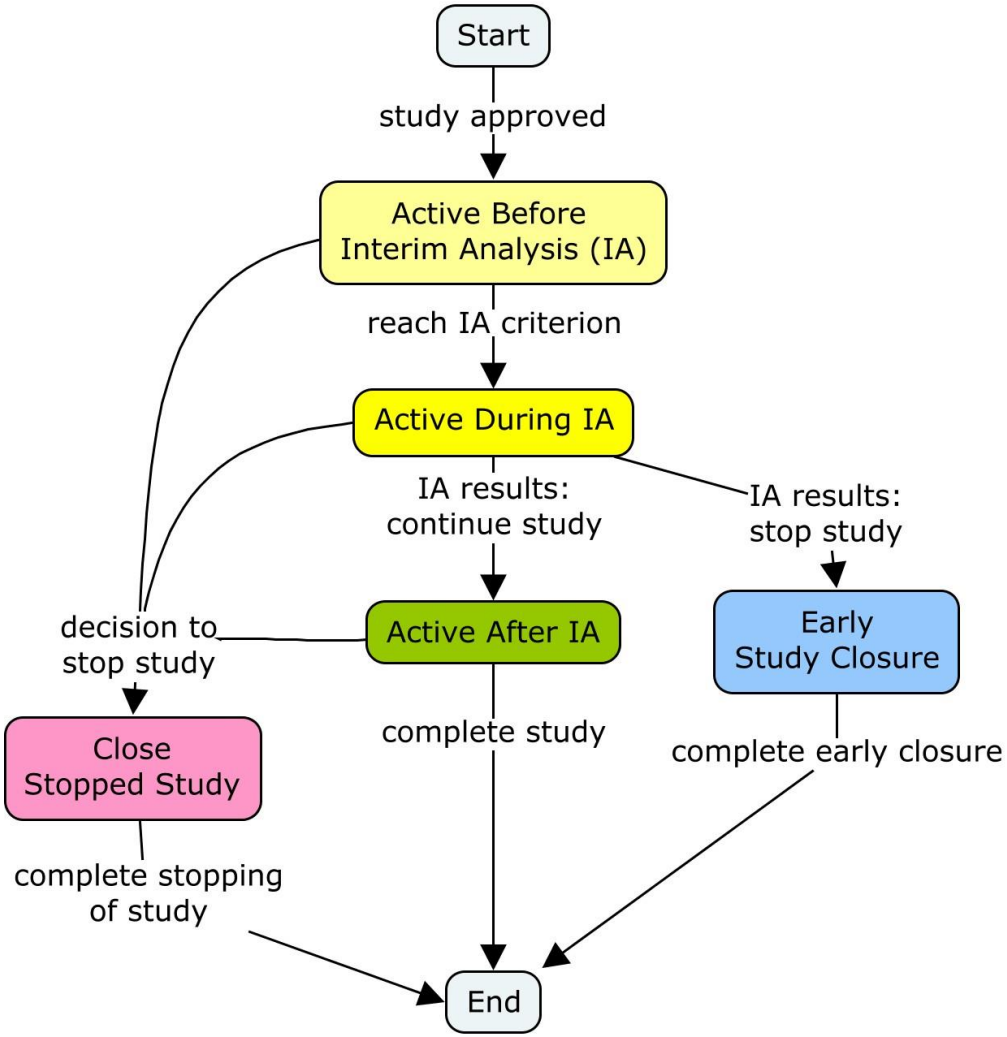
Study State Machines

- The SDTM Trial Design Model describes part of the subject state machine.
- A state machine can also be used to model what happens to a study over time.
- For example, clinicaltrials.gov uses “recruitment statuses,” including:
  - Not yet recruiting
  - Recruiting
  - Active, not recruiting
  - Completed
  - Suspended
  - Terminated
- A state machine is a model, so a study could be modeled using different sets of states (statuses).

State Machine for a Study with an Interim Analysis



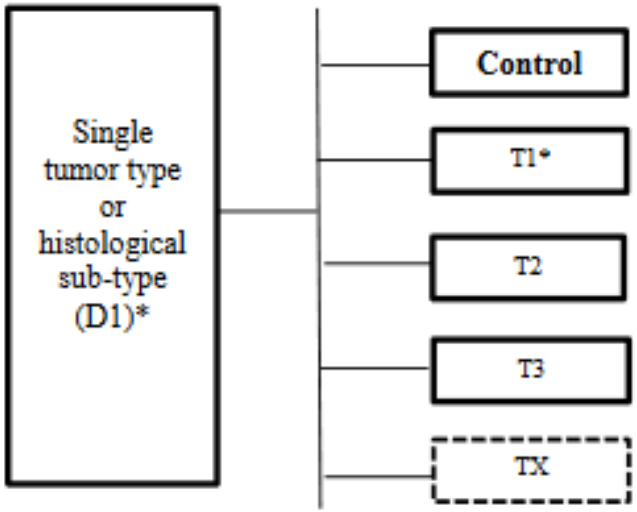
Adding Transitions for Early Study Closure



State Machines for Umbrella Trials

- In an umbrella trial the arms of the trial can change over time.
- A study state might describe the arms to which subjects are being randomized.

Figure 2: Schematic Representation of a Master Protocol with *Umbrella Trial* Design

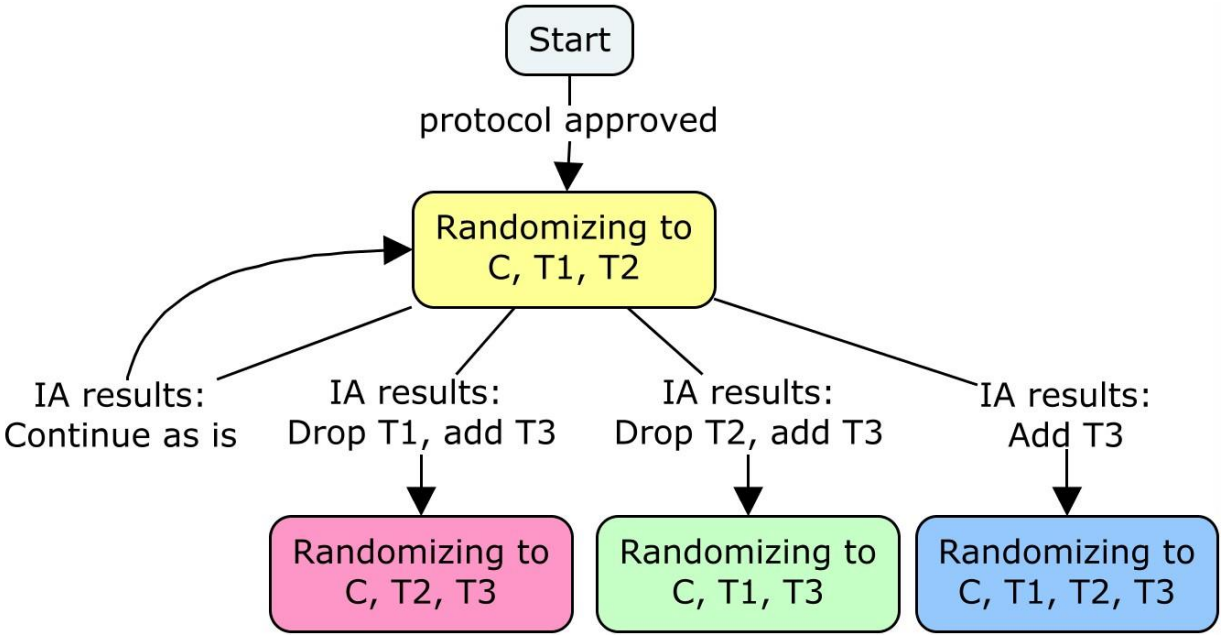


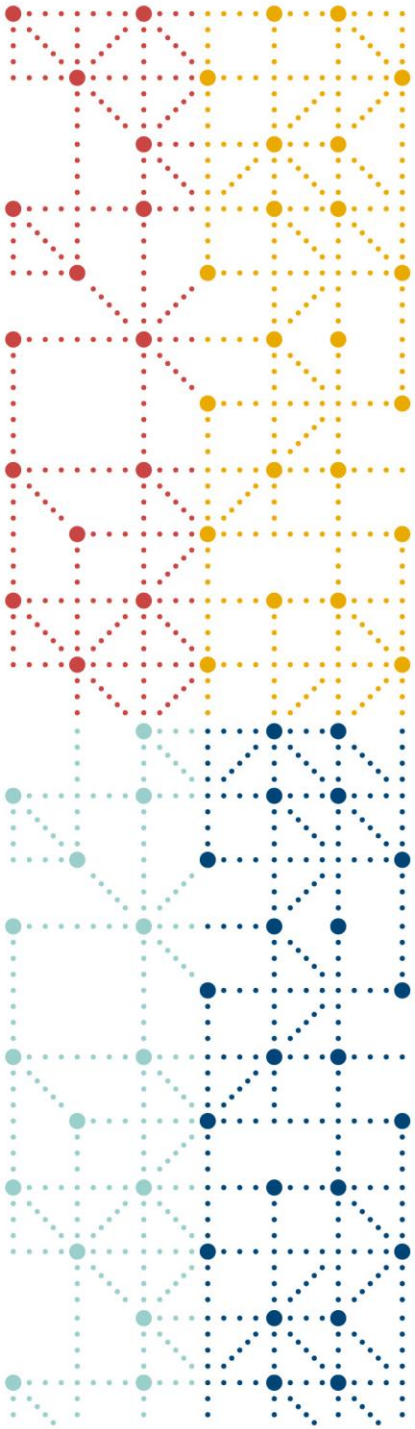
* T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border depicts future treatment arm.

Diagram from the FDA Guidance, "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biolotics"

Initial State Machine for an Umbrella Trial

- Unknown future treatments mean a complete state machine can't be built prospectively.
- This example is guessing at how interim analyses would make decisions about adding and dropping arms.





Conclusions

What Can be Represented in CDISC SDTM

- Trial Elements and Trial Arms represent treatment arms
- Arms need not be contemporaneous, e.g., arms could be dropped or added in the course of an umbrella trial.

- Trial Sets represent groupings of subjects other than treatment arms
  - Must be groupings by inherent characteristics or planned experimental factors, identified before treatment.
- For Basket Trials, Trial Sets can be used to group subjects by sub-study
  - Disease type
  - Biomarker type

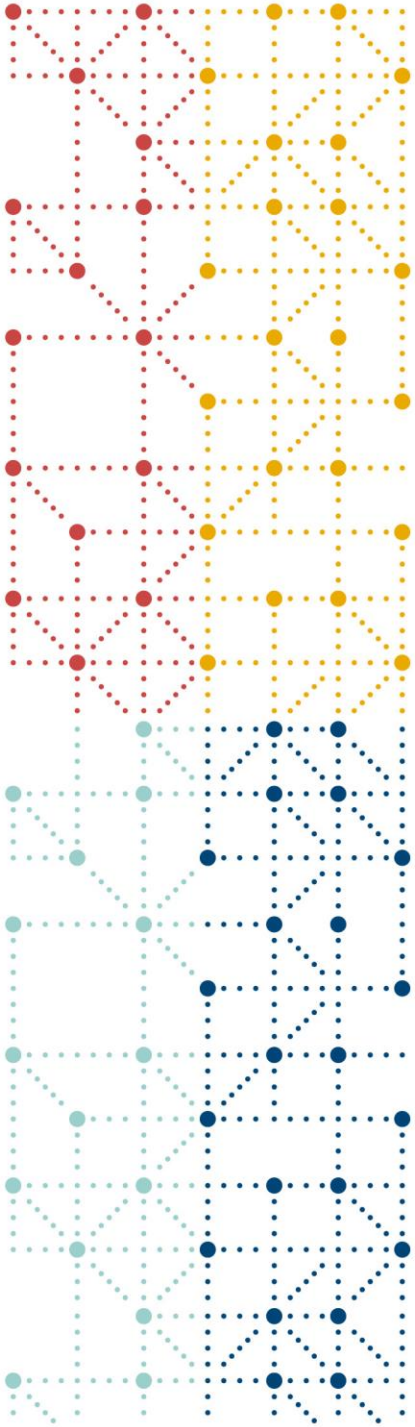
- Stopping rules can be represented in Trial Summary (TSPARM = “Study Stop Rules”)

What Can't be Represented in CDISC SDTM

- Trial Elements represents all the states in a state machine.
- Trial Arms represents only the planned state machine transitions
  - Transitions for ineligibility, early treatment stopping, early withdrawals and other things that don't go according to plan aren't included.
- TE and TA represent the states and transitions for a study subject.
- The progress of a study can also be modeled as a state machine, but this is not covered by the Trial Design Model.
  - Interim analyses are at the level of a study.
  - Dropping and adding treatment arms are at the level of a study.
- The Trial Design Model doesn't provide a state machine model for an individual site.
- The Trial Inclusion/Exclusion domain can't differentiate between eligibility criteria that apply to different subgroups in a study.

Ideas to Take Away

- Trial Sets can be used to represent groups within treatment arms.
- In a master trial with sub-studies for subjects with different characteristics, Trial Sets could be used to represent the sub-study groups.
- The Trial Elements and Trial Arms datasets are a partial representation of a subject-level state machine.
- A study-level state machine can be used to represent study changes due to interim analyses.
- A study-level state machine could be used to represent studies that add and drop arms.
  - Diagrams such as those shown could be helpful.
  - Datasets analogous to TE and TA might also be helpful, although these are not part of the SDTM.



Thank You!

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