Adaptive Clinical Trials

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Adaptive Clinical Trials

- An **adaptive design** is defined as a design that includes a prospectively planned opportunity(ies) to change the study based on accumulating data during the course of the study without undermining study integrity and validity.

- The purpose is to make clinical trials more flexible, efficient and fast.

- Flexibility does not mean that the trial can be modified any time at will.
- The modification and adaptations have to be pre-planned and should be based on data collected from the study itself.
- Analyses of the accumulating study data are performed at pre-planned timepoints within the study, with or without formal statistical hypothesis testing

The Adaptive Process

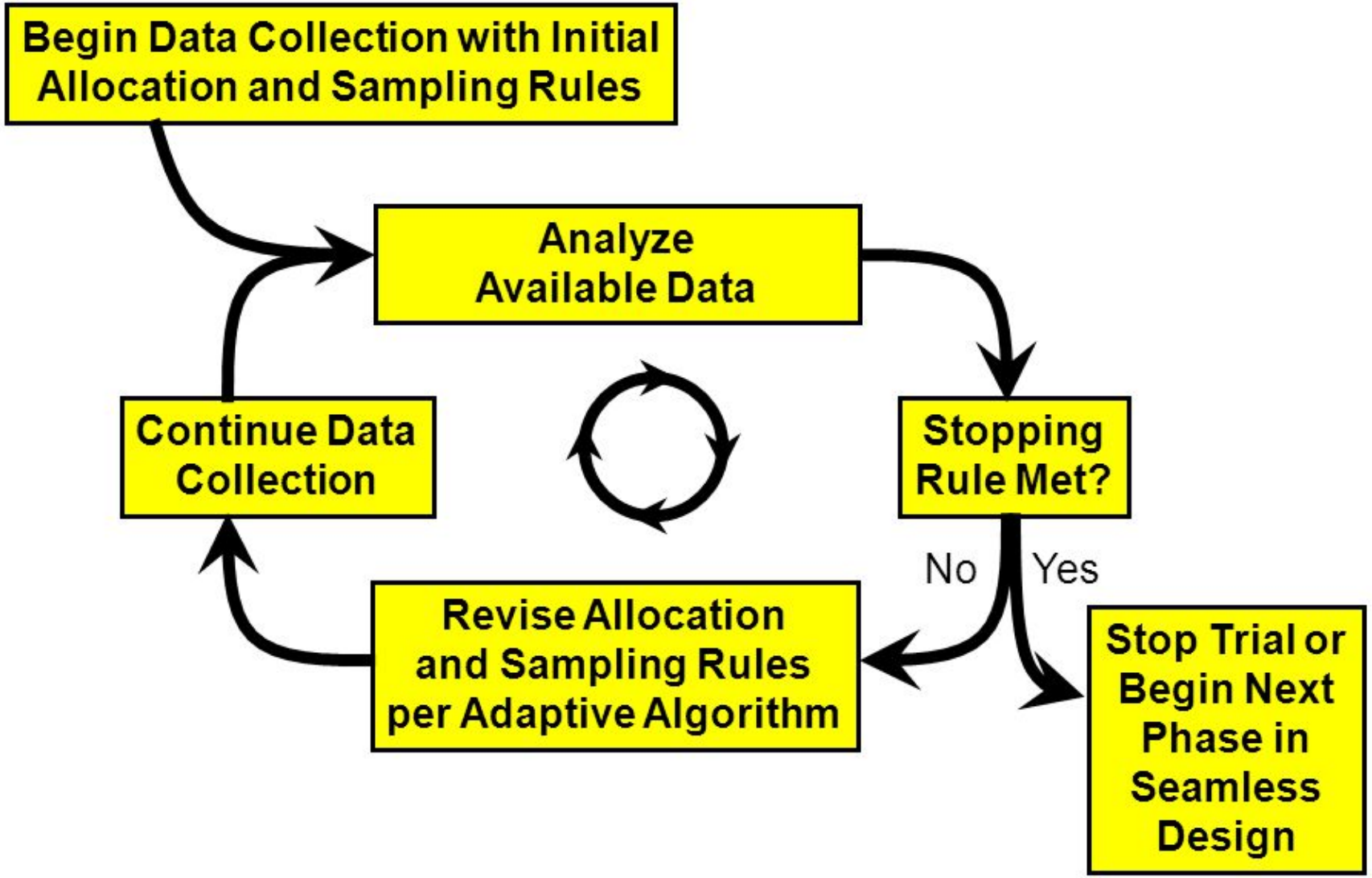


Image from Berry Consultants, LLC

Benefits of Adaptive Clinical Trials

- More efficiently provide the same (or much better) information
- Shorten development time
- Allow to correct assumptions that were made at the start of the trial if they are subsequently found to be incorrect
- Help to identify the treatments that show the most promise at an early stage in the development process
- Increase the likelihood of success on the study objective
- Yield improved understanding of the treatment's effect (e.g., better estimates of the dose-response relationship or subgroup effects, which may also lead to more efficient subsequent studies)

Adaptive Designs Currently in Use

- Continual Reassessment Method and modified CRM designs (Phase 1)
- Group-sequential design (include Simon 2-stage designs and modifications thereof)
- Response-adaptive design (include drop-the-loser / pick-the-winner design)
- Seamless phase I/II or II/III designs
- Sample size adjustments (re-estimations)
- Population enrichment
- Basket trials/ Umbrella trials

Continual Reassessment Method

- Used in dose-finding studies
- The method is based on dose toxicity models to establish what the maximum tolerated dose (MTD) of new drug is
- Dose toxicity curve is modified through out the study based on the received information
- This increases the likelihood of identifying the correct MTD
- It is also possible to add groups of participants to the trial after it has started

Group sequential designs

- The sample size of the trial is not fixed in advance, and data is sequentially evaluated as it is collected (interim analysis, might be carried out at several points in time).
- The trial can be stopped when significant results are seen, or if the interim analysis shows that there are safety concerns, or that the trial will not in fact be able to give a significant result.
- In this case no more recruitment of patients or further sampling from the patients involved will occur.

Group sequential designs

- Before the trial starts, the ‘stopping rule’ (i.e. the reason for stopping) must be documented and explained. The stopping rule is a description of exactly what the interim analysis must show to cause the trial to be stopped.
- Group sequential analysis can lead to a conclusion much earlier than would be possible with a classical design.

Response-adaptive design

- The goal of such studies is to place more patients on the better treatment based on patient responses already accrued in the trial
- Play-the winner: if treatment A appears to be more successful than treatment B thus far in the trial, than patient would have a greater than 50% chance of being assigned to treatment A
- Pick-the-winner/ Drop-the loser: start as multi-arm design to expedite the screening process and to identify the most effective drug/intervention. At the interim analysis drop the arm(s) that are less likely to succeed

Seamless phase I/II or II/III designs

- Time-to market of new therapies can be reduced by removing the time delay between phases
- Allow treatment or dose selection and comparative evaluation of efficacy with control at an interim analysis

Sample Size Adjustments (Re-estimations)

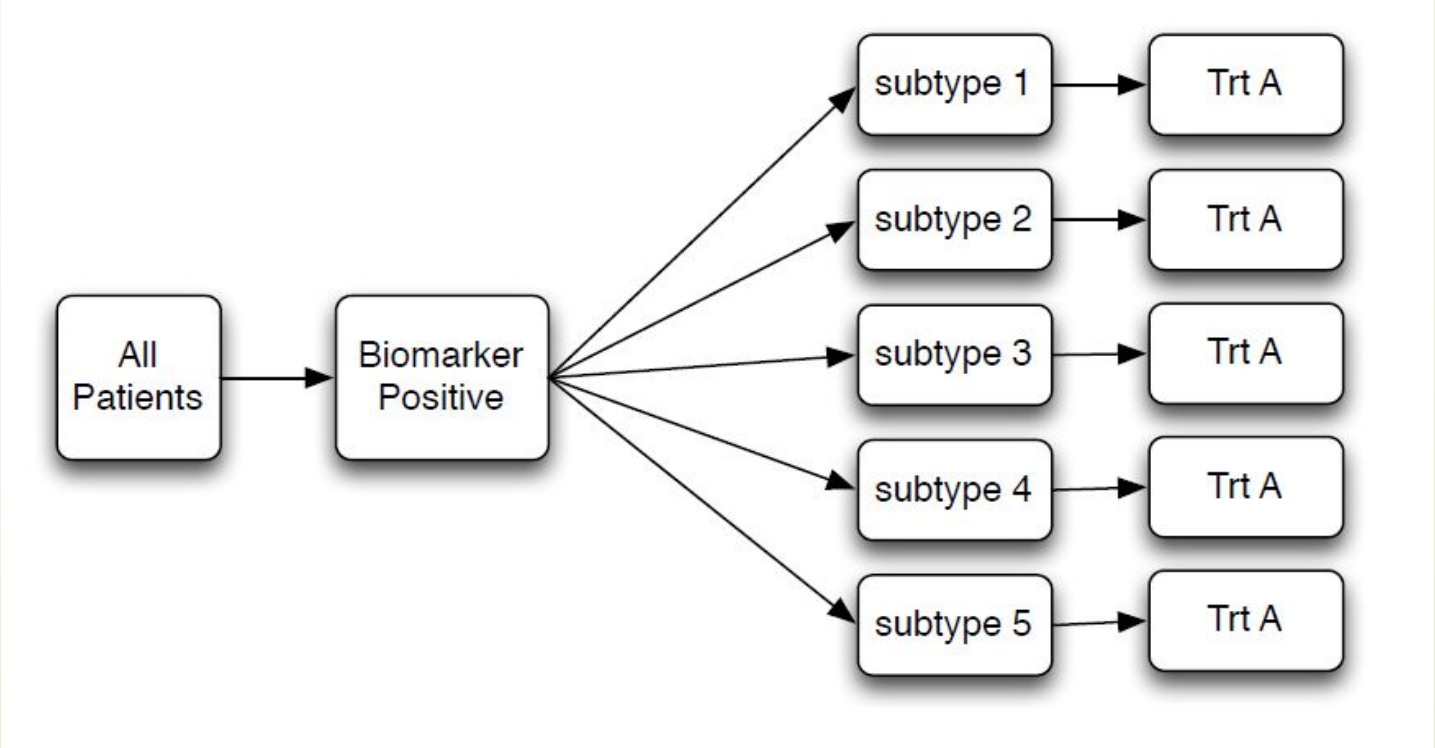
- Power calculations are based on parameters estimations done before the beginning of the trial
- Adaptive design allow sample size of a study to be reassessed in the mid-course of the study to ensure adequate power

Population Enrichment

- In this design the inclusion and exclusion criteria may be altered over time to focus on a population most likely to benefit
- Creates a single trial in which a study team can accomplish the combined task of validating a predictive biomarker and evaluating for efficacy
- Flexibility of design choices allows evaluations of efficacy to take place simultaneously for both the full population and the subpopulation with the presence of the biomarker

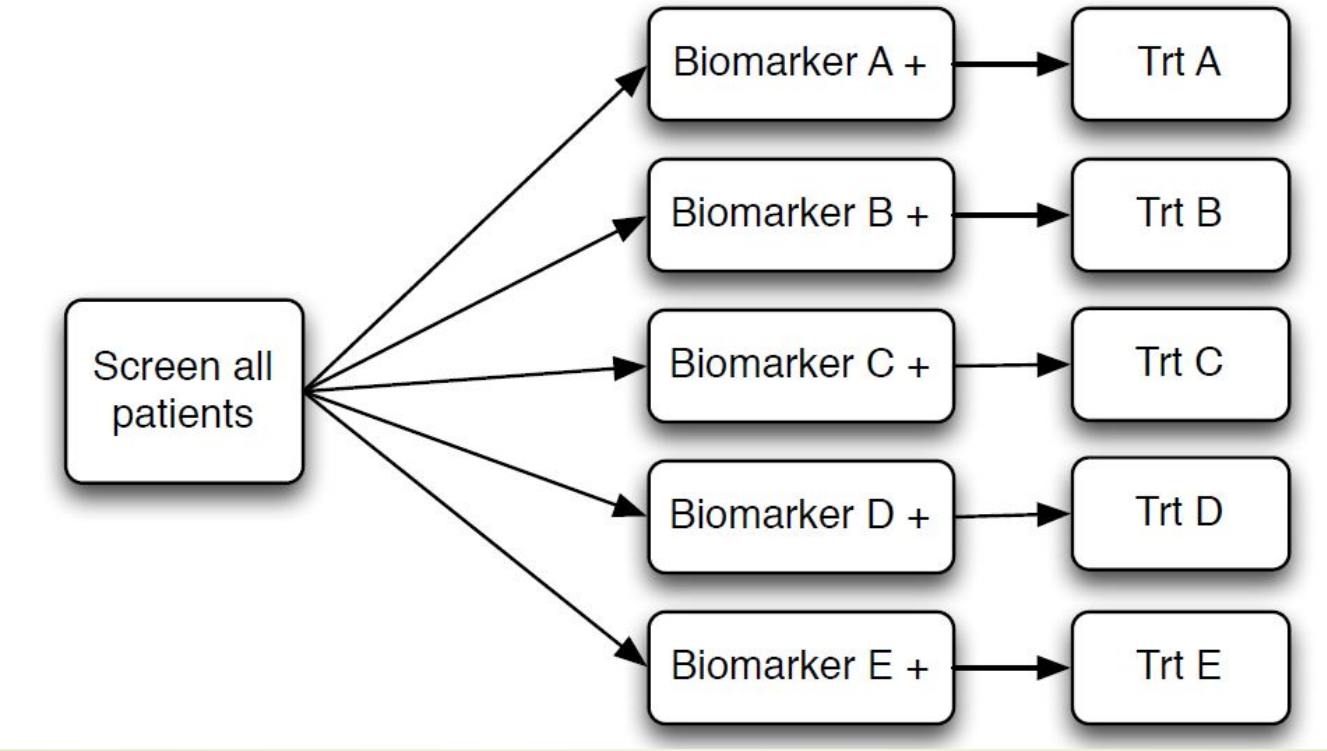
Basket trials/ Umbrella trials

- Basket trials test the effect of single treatment on a single biomarker in a variety of tumor types, at the same time
- Have the potential to greatly increase the number of patients who are eligible to receive certain drugs relative to other trials designs



Basket trials/ Umbrella trials

- Umbrella trials have many different treatment arms within one trial.
- People are assigned to a particular treatment arm of the trial based on their type of cancer and the specific molecular makeup of their cancer



Bayesian Methods in Adaptive Clinical Trials

- Adaptive designs often use Bayesian statistical methods
- Bayesian statistics uses a mathematical approach to effectively utilize prior and current information: starts with a prior belief and then uses new evidence to attain a posterior belief
- Provides a mathematical method for calculating the likelihood of a future event based on prior knowledge

Challenges with Adaptive Design

- Implementation requires more work in planning and conduct (require specialized statistical expertise, can require very prompt or real time data entry, can require very good coordination between study sites)
- Unblinded interim analyses may introduce bias
- Rapidly enrolled/ trials with delayed response may have no time for adaptations
- Major adaptations may introduce operational bias/variation to data collection
- May result in a shift in the target patient population

Clinical Trial Simulation

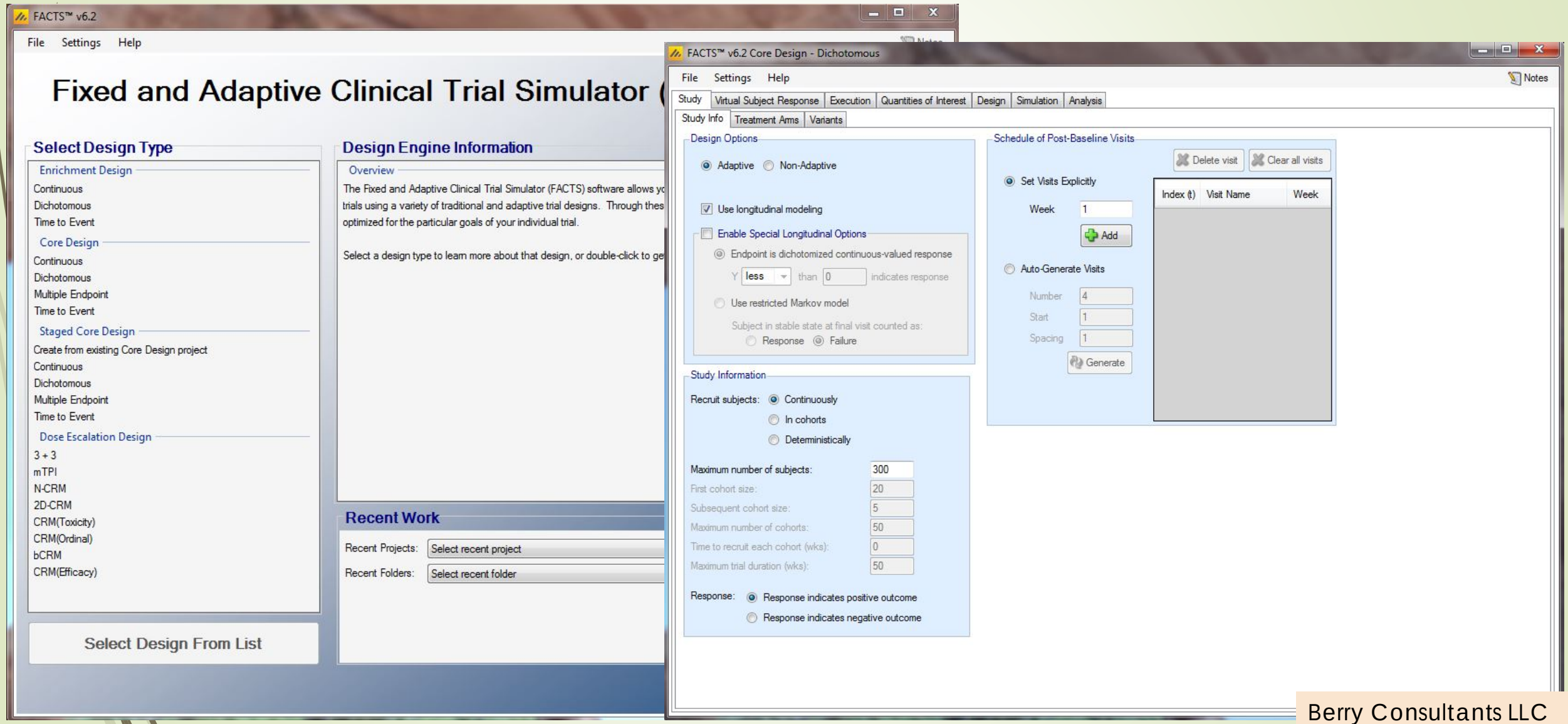
Clinical trial simulation is a process that uses computers to mimic the conduct of a clinical trial by creating virtual patients to extrapolate (or predict) clinical outcomes for each virtual patient based on the pre-specified models

Clinical Trial Simulation

Is used to:

- Monitor the conduct of the trial, project outcomes, anticipate problems and recommend remedies before it is too late
- Extrapolate (or predict) the clinical outcomes beyond the scope of previous studies from which the existing models were derived using the model techniques
- Study the validity and robustness of the trial under various assumptions of study designs

Clinical Trial Simulation - FACTS™



SURV1VE RCT, multi-national
PI: Dr. Georg Scmoelzer

Tests 2 types of cardiopulmonary resuscitation for asphyxiated newborns: standard of care (3:1 chest compression to ventilation ratio) and innovation (sustained inflation and chest compression)

Primary outcome: time to ROCS (return of spontaneous circulation)

- Sample size = 218 (109 per arm)
- 3 interim analyses at 46% (100), 67% (146), 85%(186) completion
- Stopping rule:
- Success: Posterior probability > 0.98
- Failure: Posterior probability < 0.50

SURV1VE RCT, multi-national
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	Mean N subjects	Ppn Early Success	Ppn Late Success	Total Success	Ppn Late Futility	Ppn Early Futility	Total Futility	Ppn Succ-> Fut Flip Flop	Ppn Fut-> Succ Flip Flop
Null	124.96	0.008	0.044	0.052	0.126	0.822	0.948	0	0
20% Red	164.67	0.148	0.32	0.468	0.2	0.332	0.532	0	0
25% Red	167.39	0.278	0.352	0.63	0.172	0.198	0.37	0	0
30% Red	164.65	0.448	0.366	0.814	0.098	0.088	0.178	0	0
33% Red	159.68	0.538	0.334	0.872	0.07	0.056	0.126	0	0

Type I error = alpha

power

500 simulations are run

Examples: Response-adaptive design
ECMO trial (1985)

- Extracorporeal membrane oxygenation (ECMO), a surgical procedure for newborns with respiratory failure. The technique had been used when infants were judged to be moribund and unresponsive to conventional treatment, which included ventilation and pharmacological therapy.
- Early trials on safety and efficacy indicated that the ECMO technique was safe and had an overall success rate of 56%. Historical information indicated that the conventional therapy was successful in about 20% of the cases.

Examples: Response-adaptive design
ECMO trial (1985)

- Play-the-winner rule was implemented: the first patient (1:1 chances) was assigned to ECMO and survived.
- The second patient (2:1 chances) was randomized to the conventional treatment and died.
- The third patient (3:1 chances) was randomized to ECMO and survived. All remaining patients were assigned to ECMO; all survived.
- It was decided by ranking and selection procedures that after 12 total patients had been randomized efficacy had been demonstrated; hence, the trial was stopped. Thus the PTW adaptive assignment procedure performed as intended: most patients were assigned to the treatment that appeared to be superior.