Implementing Probabilistic Baseline Adaptive Randomisations for Clinical Trials

Authors: Valarie Higgins, Vice President Clinical Services,
Ellen Shea, Associate Director Clinical Services,
Eva R. Miller, Ph.D, Associate Director, Biostatistics

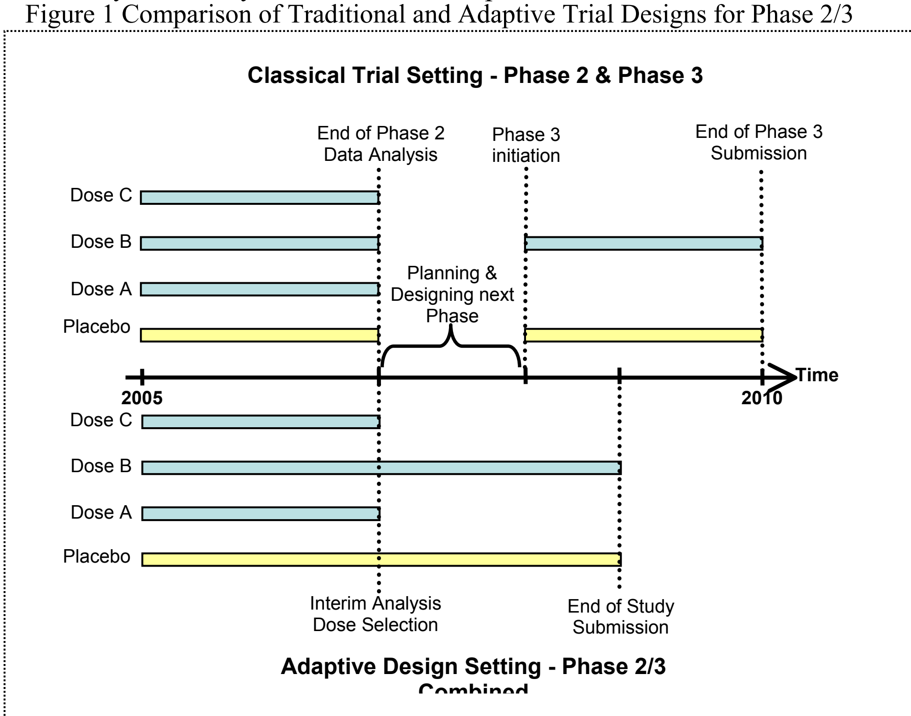
The average expenditure related to development of a drug candidate has doubled over the last decade. Each day that informed decisions about a drug candidate are delayed carries with it opportunity costs, tangible costs, and patient risk. One way to address these challenges that is receiving significant attention from pharmaceutical companies and regulatory agencies throughout the world is adaptive trial design and the use of technologies to implement these designs.

.

Adaptive Trial Design Overview and Benefits

The classic challenge of developing new medical treatments while minimizing patient safety risk is nothing new to the pharmaceutical industry. However, due to steeply rising drug development costs and escalating patient safety concerns, there is increasing pressure on pharmaceutical companies and industry thought leaders to reexamine traditional clinical trial techniques and find ways to increase the efficiency and safety of the clinical trial process.

Figure 1 Comparison of Traditional and Adaptive Trial Designs for Phase 2/3



One way to address these challenges that is receiving significant attention from pharmaceutical companies, regulatory agencies, and industry thought leaders is adaptive trial design. Adaptive trial design refers to a conceptual clinical trial methodology which allows for modifications to take place after the trial has started without compromising the scientific method. Examples of adaptive trial modifications include balancing based upon probabilistic baseline adaptive randomization, combining phases one and two (Figure 1), dropping a treatment arm, modifying the sample size, or simply stopping a study early for success or failure. For all forms of adaptive design, the important distinction that is critical to maintaining the research perspective is that the decision-making rules governing the adaptation must be clearly stated in the protocol.

Dr. Dragalin[1] recently offered a very clear definition of Adaptive Design as one which uses accumulated data to decide on how to modify aspects of the study without undermining the *validity* and *integrity* of the trial. He further delineated the general structure of an adaptive clinical trial as:

- An adaptive design requires the trial to be conducted in several stages with access to the accumulated data
- An adaptive design may have one or more rules:
    - Allocation Rule: how subjects will be allocated to the available arms
    - Sampling Rule: how many subjects will be sampled at next stage
    - Stopping Rule: when to stop the trial (for efficacy, harm, futility)
    - Decision Rule: the final decision and interim decisions pertaining to design change not covered by the previous three rules
- At any stage, the data may be analyzed and next stages redesigned taking into account all available data

An adaptive design should be adaptive by ‘design’ not an *adhoc* change of the trial conduct and analysis. Adaptation is a definite feature, not a remedy for poor planning.

Each of these adaptive design components revolves around a core mission of allowing clinicians to maximize the safety and efficacy information that is generated from each subject. This mission is especially critical in the case of studies involving medical devices, surgical procedures, terminally ill patients, orphaned drugs, and rare conditions. In these clinical situations, small available patient populations make maintaining balance among treatments for the analysis population and subgroups especially challenging.

By applying probabilistic baseline adaptive randomization, a form of adaptive design, better balance can be achieved in small study situations, or large studies with many subgroups, than is possible using simple randomization or traditional minimization techniques. Probabilistic baseline adaptive randomization is different from the minimization techniques introduced in the 1970’s in that some element of chance is applied to every randomization decision, not just for tie-breaking decisions. This is an important distinction because the methodology is then probabilistic, rather than deterministic.

As has been clearly documented in the literature, simple stratified randomization is of limited utility if many strata result in too few subjects per stratum[2,3,4]. With probabilistic baseline adaptive randomization, consideration is given to the hierarchy of balancing decisions or the weights of prognostic factors. Hierarchical ordering of prognostic factors or weights of factors may be derived from previous clinical trials or preliminary data.

Probabilistic baseline adaptive randomization is best implemented using a phone or internet based interactive clinical technology in today’s research and regulatory environment. These technologies allow for more accurate and efficient implementation of the adaptive randomization designs. Adaptive designs require real time data in order to determine each randomization. The use of interactive technologies enables this data to be collected and utilized in the randomization process through a validated system, ensuring the integrity and success of the algorithm.

The Development and Implementation of the Random Adaptive Algorithm

Adaptive randomization designs have been implemented in clinical trials since the 1970s, and at first with computational techniques that seem quite primitive, by today's standards. Statisticians have learned that in order to ensure that the intended randomization objectives will be met, each random adaptive algorithm requires an extensive series of planning and verification steps.

After the primary efficacy endpoint and analytical model are determined, the appropriate factors to include in the random adaptive algorithm must be established. As a starting point, information about prognostic factors can be derived from clinical judgment, previous studies or historical values reported in clinical literature. After prognostic factors (at baseline) are chosen, decisions need to be made about the nature of the statistical methodological framework, the priority or weight given to each factor within the decision-making rule (even the decision not to use weights actually means that all factors are equally important), and choice of proportional assignments among treatment groups. Rosenberger and Lachin offer some excellent detailed statistical explanations on adaptive randomization model development[6]. The contributions of the prognostic factors, their hierarchical structure and/or their weighting and how these impact balance need to be thoroughly tested. Currently, there is no set of rules for the statistician to use to develop the single definitive random adaptive algorithm or decision making rule; therefore, a goodly amount of thought and work goes into this process for each clinical trial protocol. An adaptive randomization algorithm which follows either a classical or Bayesian theoretical framework is clearly delineated through simulation testing. It is generally agreed that the algorithm selected must demonstrate a high level of convergence for the balancing criteria.

Once the design of the randomization strategy has been established, your interactive technologies vendor should work directly with the client to develop system requirements for the random adaptive algorithm. It is best to perform simulation testing during the development phase of the random adaptive algorithm system module to:

- Address the robustness of the random adaptive algorithm to conditions not under the researcher's control, especially the order in which the subjects enroll[2]. As Pocock and Simon stated, the random adaptive algorithm must accommodate this form of variation that is not under the investigator's control. "Re-sequencing" -- a technique for reordering seeded data in a simulation and checking the resultant balances while holding the random adaptive algorithm and random numbers constant -- is applied.

- Verify the degree to which chance alone will alter the overall balance and the balance for strata or subgroups. This may be accomplished by using multiple randomization schedules against the same simulation data set. Some authors refer to this as "re-randomization".

Figure 2 An Example of a Probabilistic Baseline Adaptive Randomization Design Implementation

Adaptive Randomization Using Urn Randomization Methodology
Attenuated Example with Two Factors, Factor 1 and Factor 2
Three Treatment Groups Representing Different Levels of Active Drug — Active Drug

Note to file: from Simulation 2

Subject ID:	111112049
Site Number:	22
s=	0
x=	1

Note: If {A+B+C} = 0 then go directly to decision making rules in cells J13..K15.

Note: Enter all seven rand count values for each patient being randomized.

	Treatment A	Treatment B	Treatment C
Factor 2: Low level			
Factor 1(i)		1	8
Factor 2: Middle level			
Factor 1(i)	9	6	7
Factor 2: High level			
Factor 1(i)	9	8	

Factor 2: Middle level	Treatment A	Treatment B	Treatment C
A=	2	2	2
B=	2	2	2
C=	1	1	1
D=	0	0	0
E=	0	0	0
F=	1	1	1
G=	2	2	2
H=	2	2	2
I=	0.375	0.3125	0.3125
J=	0.3333	0.3333	0.3333
K=	-0.0417	0.0208	0.0208
L=	-0.0833	0.0417	0.0417
$P_{(T)}$ =	0.2500	0.3750	0.3750
neg. corrected $P_{(T)}$ =	0.25	0.375	0.375
$P''_{(T)}$ =	0.25	0.375	0.375

Adaptive Randomization Using Urn Randomization Methodology
Attenuated Example with Two Factors, Factor 1 and Factor 2
Three Treatment Groups Representing Different Levels of Active Drug — Active Drug

Subject ID:	111112049	Factor 1: Level 2
Site Number:	22	Factor 2: Middle leve

Next sequencial number from rand list:	Random Number:	Treatment Arm Assigned:
520	0.3789	B

Condition	Rule		Assign:
If A = B = C = 0			
	0.0001 ≤ random number < 0.3333	0.3333	A
	0.3333 ≤ random number < 0.6667	0.6667	B
	0.6667 ≤ random number < 1.0000	1.0000	C
Factor 2: Low level			
	0.0001 ≤ random number ≤ 0.5000	0.5000	B
	0.5000 ≤ random number < 1.0000	1.0000	C
Factor 2: Middle level			
	0.0001 ≤ random number < 0.2500	0.2500	A
	0.2500 ≤ random number < 0.6250	0.6250	B
	0.6250 ≤ random number < 1.0000	1.0000	C
Factor 2: High level			
	0.0001 ≤ random number < 0.4000	0.4000	A
	0.4000 ≤ random number < 1.0000	1.0000	B

- Validate the implementation within the phone or internet based interactive clinical technology by verifying that all boundary values are correct, that definitions stated in the algorithm are appropriately programmed, and that the information from the randomisation module about each patient is being appropriately captured.

Randomization reports should also be designed to facilitate the decision-making process by showing resultant balances overall and for subgroups or strata. Also, individual listings of subjects randomized (in simulations and later in the live study) should show the stratification factors of the subjects, the randomization counts upon which the treatment assignment was made, the random number, the probabilities, and the logical decision making rules (in footnotes).

Urn Randomization: A Case Study

Urn randomization was introduced by Wei[7,8,9], a Bayesian statistical theorist. In urn randomization the assignment of probabilities is adapted to the degree of imbalance in relation to the number of patients already entered into the trial. Schoeten[5] describes an even more flexible urn model than that described by Wei. Schoeten's model, called biased urn randomization, is especially useful because it is appropriate for small sample sizes and when blinding is not feasible.

Our real-world example clinical-trial was for a rare medical condition; the clinical trial had three treatment groups representing different dose levels of the active study drug (see Figure 2). Given the rare medical condition, the total anticipated sample size was small (under 50 subjects). The design called for one continuous factor (Factor 1) with two levels to be considered. The design is particularly interesting because it required attenuation of a second continuous factor (Factor 2) for clinical considerations: only treatments A and B were administered to patients in the highest level of Factor 2, and only treatments B and C were administered to patients in the lowest level of Factor 2. Balancing was not required for Factor 2; it was used to accomplish the desired clinical dose regulated attenuation. Balance within this randomization design was achieved overall and for Factor 1.

As shown in the example above, probabilistic baseline adaptive randomization is especially easy to tailor to specific protocols.

Enabling Technologies

While adaptive design thought leaders differ on a number of theoretical statistical issues, nearly every adaptive design thought leader agrees upon the critical role that technology plays in support of adaptive design implementation. In the case of probabilistic baseline adaptive randomization, a phone or internet based interactive clinical technology is essential. In the broader context of adaptive trial design, other technologies including eCRFs or electronic data capture (EDC), and clinical supply forecasting technologies also play a key role.

EDC and phone or web based Interactive clinical technologies provide the adaptive decision makers the ability to rapidly report on accumulated data that are required to be analyzed to determine adaptive trial decisions and next phase design. Without the use of these tools, obtaining the data required for analysis could take months as opposed to hours or minutes.

In addition to enabling quicker data analysis, the use of phone or web based Interactive clinical technologies along with a clinical supplies forecasting tool is key to the success of Adaptive Supply Management (ASM). These tools allow for quick response to changes in supply demand that may result from adaptive trial decisions. Forecasting reports that show immediate and precise supply need at multiple levels of the trial (overall, depot and site) as well as future supply need can be preconfigured so that they can be provided to the Clinical Supply Manager as soon as the adaptive trial decisions are available. A diagram of how these technologies interrelate is shown in Figure 3.

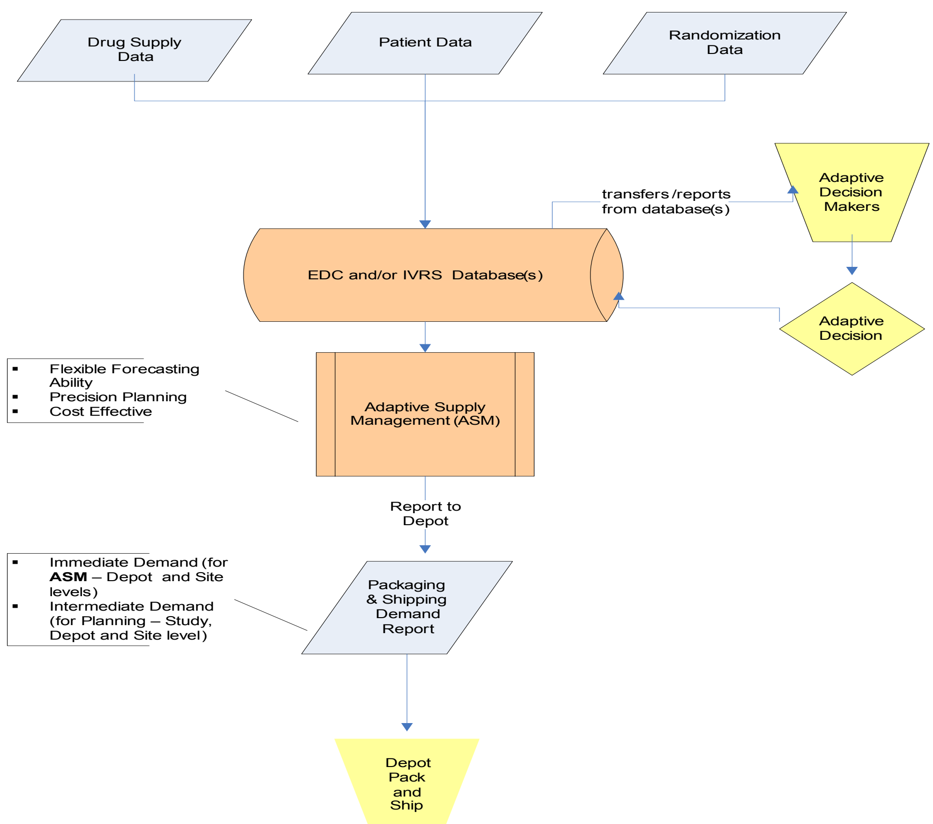
Conclusion

Many thought leaders in the industry have demonstrated that Adaptive Trail Designs can be instrumental in increasing the efficiency and safety of the clinical trial process. With well developed and designed technology, these designs can be efficiently and successfully implemented.

One of the most common methods of Adaptive Trial Design is the use of adaptive randomization. Baseline adaptive randomization approaches are flexible, easy to customize for specific clinical trial statistical designs and easy to implement using phone or internet based interactive clinical technology. While planning and implementing probabilistic baseline adaptive randomization does require significant effort, the benefit that is achieved by maximizing the safety and efficacy information generated from each patient results in a high return on investment.

Many applications of Adaptive Trial Designs result in the need for flexible and responsive clinical supplies management, Adaptive Supply Management (ASM). EDC, Interactive clinical technologies and clinical supplies forecasting tools are key to the success of Adaptive Supply Management (ASM).

Figure 3 Use of Enabling Technologies for Adaptive decisions & ASM



References

1 V Dragalin 'Classification of Adaptive Designs', presentation IBC 2nd Annual Adaptive Designs Conference, Princeton, NJ November 7, 2005.

2 SJ Pocock, R Simon. 'Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial', ***Biometrics*** 31, pp 103-115, 1975.

3 SJ Pocock. *Clinical Trials, a Practical Approach*. Chapter 5, Chichester: Wiley, 1983.

4 T Therneau. 'How many stratification factors are "too many" to use in a randomization plan?' ***Controlled Clinical Trials*** 14: 98-108, 1993.

5 HJA Schouten. 'Adaptive biased urn randomization in small strata when blinding is impossible', ***Biometrics,*** 51, pp 1529-1535, 1995.

6 WF Rosenberger, JM Lachin. Randomization in Clinical Trials: Theory and Practice. Wiley, 2002.

7 LJ Wei. 'A class of designs for sequential clinical trials', ***Journal of the American Statistical Association*** 72: pp 382-386, 1977.

8 LJ Wei. 'An application of an urn model to the design of sequential controlled clinical trials', ***Journal of the American Statistical Association*** 73: pp 559-563, 1978.

9 LJ Wei. 'Properties of the urn randomization in clinical trials', ***Controlled Clinical Trials*** 9: pp 345-364, 1988.

The authors can be contacted at eva.miller@icti-global.com, and valarie.higgins@icti-global.com