INNOVATIVE STATISTICAL DESIGN & ANALYSIS IN PD

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OVERVIEW

The traditional approach to clinical trials tends to be large, costly, and time-consuming.

There is a need for more efficient clinical trial design, which should lead to an increased chance of a “successful” trial that answers the question of interest.

Hence, there is increasing interest in innovative trial designs.

For example, *adaptive designs* allow reviewing accumulating information during an ongoing clinical trial to possibly modify trial characteristics.

OVERVIEW

General agreement that changes should be based on *pre-specified* decision rules.

"Adaptive By Design"

Properly designed simulations are often needed to confirm adaptations preserve the integrity and validity of study.

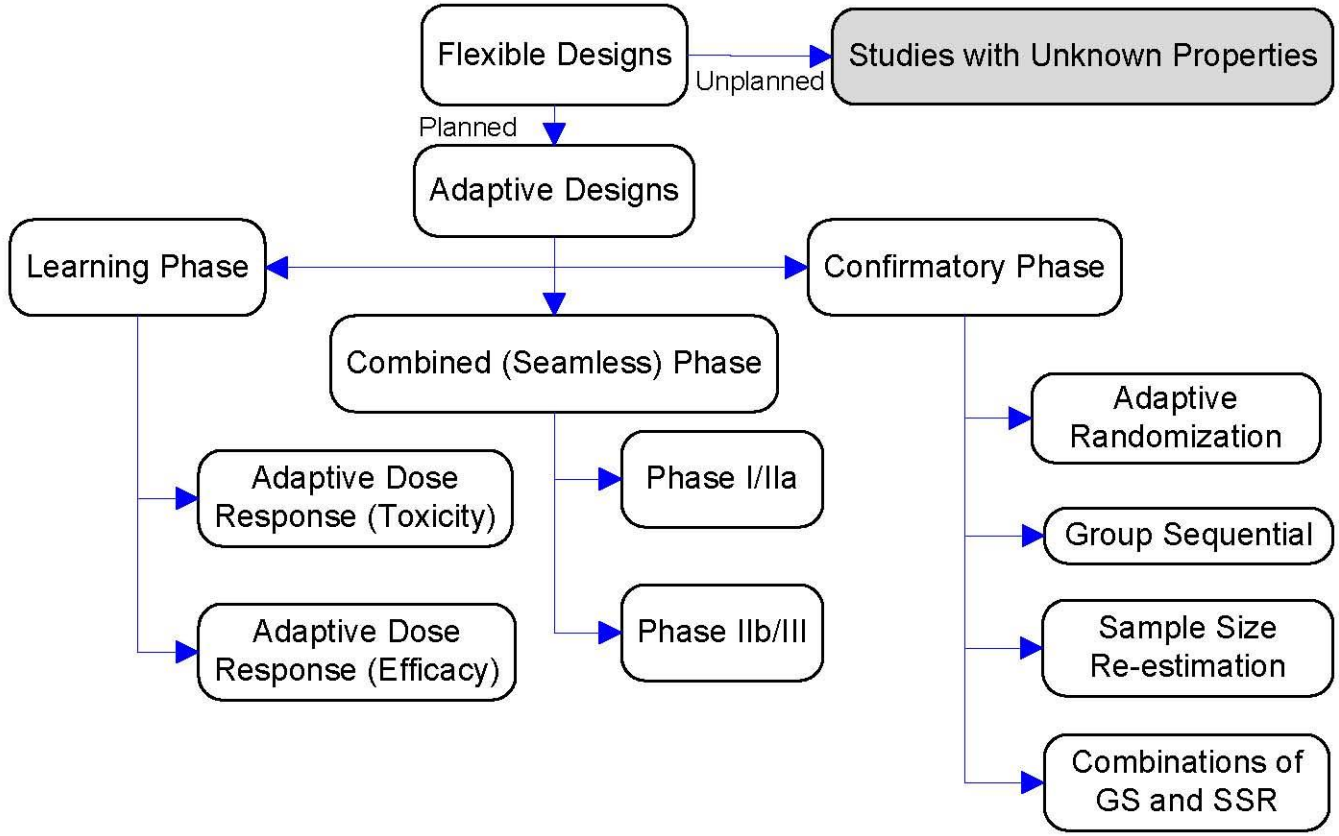
In order to properly define the simulations, adaptation rules must be clearly specified in advance.

Thus, only planned adaptations can be ***guaranteed*** to avoid any unknown bias due to the adaptation.

Adaptive Design Working Group (Gallo et al, 2006)
FDA "Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics" (2010)
FDA "Guidance for Industry: Adaptive Designs for Medical Device Clinical Studies" (2016)

OVERVIEW

Infinite number of adaptive design possibilities:



Source: Kairalla JA, Coffey CS, Thomann MK and Muller KE (2012). Trials, 13: 145.

"CONFIRMING STAGE" ADAPTATIONS

Scrutiny of protocol will vary depending on design proposed.

From FDA perspective, some confirmatory designs are considered "well understood" – need no statistical correction or have been studied in sufficient detail that proper statistical corrections exist.

Important to note "less well understood" designs based only on current experiences at FDA (not level of acceptability).

Hence, "less well understood" methods are not automatically prohibited by FDA – but, higher bar for justifying designs.

Providing lack of bias and proper operating characteristics requires extensive planning and validation.

ENRICHMENT DESIGNS

An *adaptive enrichment design* fulfills the desire to target therapies to patients who can benefit the most from treatment.

In such designs, a trial initially considers a broad population.

The first study period reveals participant groups most likely to benefit from treatment (discovery phase).

Subgroup members are then randomized to treatment groups (validation phase).

Hence, study power is increased (sample size decreased) by focusing only on subgroups most likely to show benefit.

SAMPLE SIZE RE-ESTIMATION

A *sample size re-estimation* (SSR) design refers to an adaptive design that allows for adjustment of sample size based on a review of the interim data.

An internal pilot (IP) design refers to an SSR used to reassess nuisance parameters (only) mid-study.

With moderate to large sample sizes, IP designs can be used to make appropriate modifications with minimal (if any) inflation of type I error rate.

Thus, there is little reason (statistically) not to do this for most clinical trials!

MDS-UPDRS TOTAL – SAMPLE SIZE

Hypothetical Early PD Clinical Trial:

- Required sample size for detecting change in MDS-UPDRS OFF scores over 1 year (using PPMI Data)

TIME	Mean (SD) Change From Baseline	Power	Reduce by 50%	Reduce by 25%
All	7.5 (11.6)	80% 90%	310 410	1250 1650
Treated	5.0 (12.0)	80% 90%	720 960	2850 3800
Untreated	10.0 (10.6)	80% 90%	150 200	570 760

MDS-UPDRS TOTAL – SAMPLE SIZE

Hypothetical Clinical Trial:

- Power greatly impacted by frequency of subjects who start therapy within the 1 year period
- Can base sample size calculation on ‘best guess’
- Two adaptive options:
  - Enrichment Design:
    - Identify those unlikely to require treatment during first year
  - Internal Pilot Design:
    - After some fraction of subjects have completed one year of follow-up, estimate the percentage starting therapy
    - If different from original assumption, re-estimate sample size based on revised estimate

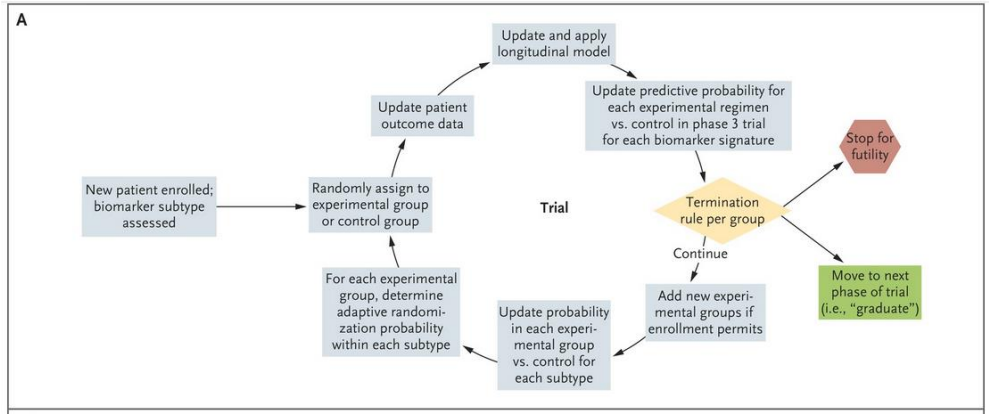
PLATFORM TRIALS

Platform trials allow for concurrent evaluation of multiple treatments – more efficient than traditional two-arm trials.

- Goal is to find best treatment by simultaneously investigating multiple treatments.

Use pre-specified stopping boundaries to determine if experimental treatment arms should be dropped.

Treatment arms can be added as trial progresses.



Source: Rugo et al (2016). New England Journal of Mediciine, 375: 23-34.

ADAPTIVE SEAMLESS DESIGNS

An adaptive seamless design combines objectives traditionally addressed in separate trials into a single trial.

- Participants enrolled in first stage are used to inform the second state.
- Final analysis uses data from participants enrolled in both stages in the final analysis.

Since data from first stage informs decisions about second stage, using all data in final analysis raises concerns about bias and error rate inflation.

Data from both stages must be combined in a way that guarantees key statistical operating characteristics.

ADAPTIVE SEAMLESS DESIGN - EXAMPLE

Phase II Trial of CoQ10 for ALS Finds Insufficient Evidence to Justify Phase III

Petra Kaufmann, MD, MSc,[1] John L.P. Thompson, PhD,[1,2] Gilberto Levy, MD, MS,[2] Richard Buchsbaum,[2] Jeremy Shefner, MD,[3] Lisa S. Krivickas, MD,[4] Jonathan Katz, MD,[5] Yvonne Rollins, MD, PhD,[6] Richard J. Barohn, MD,[7] Carlayne E. Jackson, MD,[8] Ezgi Tiryaki, MD,[9] Catherine Lomen-Hoerth, MD, PhD,[10] Carmel Armon, MD,[11] Rup Tandan, MD,[12] Stacy A. Rudnicki, MD,[13] Kourosh Rezania, MD,[14] Robert Sufit, MD,[15] Alan Pestronk, MD,[16] Steven P. Novella, MD,[17] Terry Heiman-Patterson, MD,[18] Edward J. Kasarskis, MD, PhD,[19] Erik P. Pioro, MD, PhD,[20] Jacqueline Montes, PT, MA,[1] Rachel Arbing, MPH,[2] Darleen Vecchio, MS,[1] Alexandra Barsdorf, MA,[1] Hiroshi Mitsumoto, MD,[1] and Bruce Levin, PhD[2]; for the QALS Study Group

Objectives of this trial:

1. Select which of two doses of CoQ10 (1800 or 2700 mg/day) is preferred
2. Determine if sufficient evidence of efficacy to justify conducting a large phase III efficacy trial using dose selected at stage 1

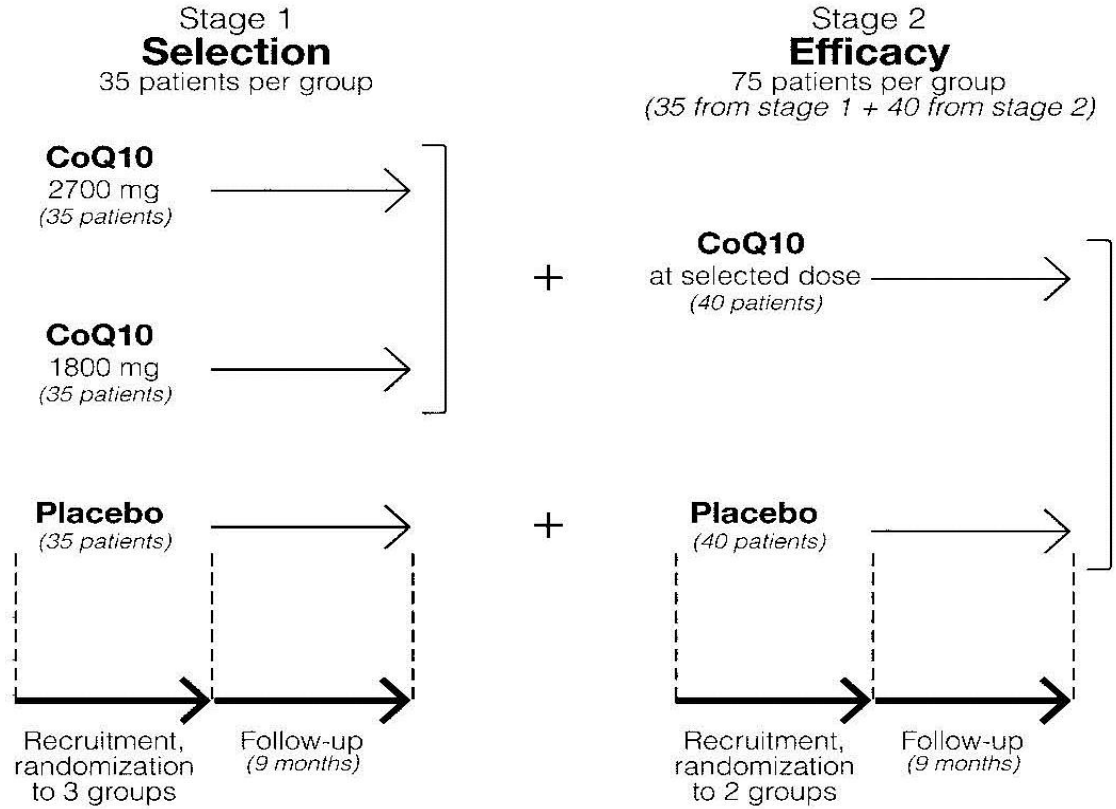


Figure. Two-stage phase II design of the Clinical Trial of High Dose Coenzyme Q10 in ALS (QALS study; total: 185 patients, 105 in stage 1 and 80 in stage 2).

BARRIERS TO USE OF AD's

One common misconception is that an AD requires less planning than a standard trial design.

On the contrary, consideration of an AD generally requires more upfront planning for evaluating alternative designs.

Properly planned ADs may lead to more efficient trials requiring less time / fewer resources than traditional designs.

But, ADs are not always better – time required to do simulations and justify the design may offset any 'time' saved by the adaptations.

One should use ADs only when necessary.

BARRIERS TO USE OF AD's

To address this issue, there has been a movement towards creating in-house teams primarily responsible for conducting such simulations.

Survey findings showed that many have some form of AD working group within their organization:

- 64% Pharmaceutical/biotech companies
- 100% CRO's
- 0% Academic groups

Source: Morgan et al (2014). Therapeutic Innovation & Regulatory Science, 48(4): 473-481.

BARRIERS TO USE OF AD's

Greater barriers exist for implementing this type of infrastructure within the publicly funded environment.

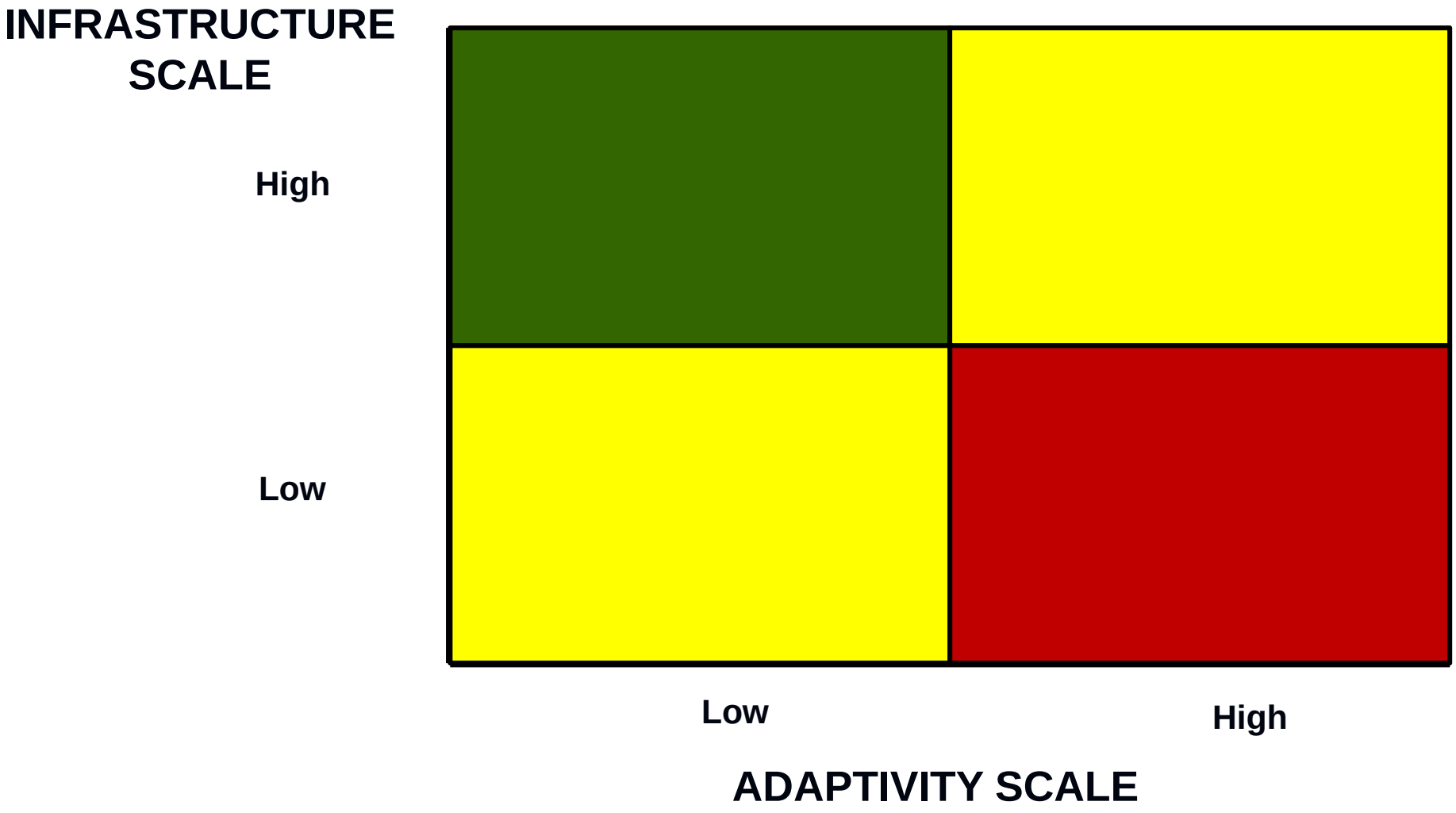
For example, grant applications require these simulations to conducted before design is finalized – i.e., before grant submission.

Few mechanisms exist to support these complex simulations.

Consequently, growing divide between the practicality and feasibility of conducting ADs in industry vs. academia.

Acceptance of ADs (and other types of innovative trial designs) in general will depend on increasing their use and acceptance across all types of clinical trials.

BARRIERS TO USE OF AD's



NeuroNEXT

Clearly, infrastructure building efforts are needed to help further advance the use of AD's.

One recent example of developing infrastructure to address this problem is the creation of the NINDS-funded Network of Excellence in Neuroscience Clinical Trials (NeuroNEXT).

Network designed to implement projects initiated by investigators from academia, industry, and foundations – experienced or early in career.

NeuroNEXT

Novel initiatives of NeuroNEXT:

- Utilization of a Central IRB of record (CIRB)
- Pre-existing Master Clinical Trial Agreements (MCTA) between clinical coordinating center and all clinical sites
- **Availability of experienced trial design staff to assist with protocol and grant development**
  - This infrastructure dramatically increases the feasibility for using more novel trial designs – including adaptive designs

SUMMARY

Statistical development is well fleshed out for the use of adaptive designs.

However, despite their suggested promise, current acceptance and use of ADs in ongoing clinical trials is not aligned with attention given ADs in the literature.

A number of logistical barriers must be addressed.

Currently, pharmaceutical industry is well ahead of academic trialists with respect to addressing these barriers.

SUMMARY

It is important to be clear about what an adaptive design can and cannot do.

An AD cannot “change the answer” regarding the effectiveness of a particular treatment, but can increase the efficiency in finding an answer.

An AD design ***cannot*** make a drug more effective.

Rather, one of the biggest benefits of an AD is ability to identify ineffective treatments in a more timely manner.