Adaptive Design Considerations: A Regulatory Perspective on How to Maintain Validity and Integrity of Trials*

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Outline

- Historical Background
- Trial Logistics Models
- Some Examples on Data Integrity Issue
- Follow-up on Real-Time Inspection
- Concluding Remarks

Changes in Fixed Design ?

Making sure changes meant to be ***blinded*** are blind

- Fixed design in A&WC trial by definition pre-specifies study objectives and critical design parameters
- However, we are seeing increasing number of trials with changes in SAP at or beyond study completing date – protocol amendment, but, is it reactive adaptation?
- **We ask for evidence of blinding, but it's a major problem**
- It is critical to establish the infrastructure that fully defines and describes 'firewalls' in place and assures unbiased changes

Group Sequential Design
Beginning of Adaptive Design

- Randomized clinical trials designed with stopping boundary
  - For early efficacy or futility
- Concept of DMC as a formal committee first introduced in 1967
- Role of DMC: review accumulating study data as trial progresses to monitor safety, effectiveness, and trial conduct issues in a set of recommendations to sponsor (CCT, 1988)
  - **Not individuals closely involved with design & conduct**
  - Expert advisors external to trial organizer, sponsor, investigators, **who can be fully objective** in reviewing the interim data for any emerging concerns – **not intended to make adaptive recommendation of adaptive design trial**

Principles for Adaptive Design

Adhere to Scientific and Statistical Rigor that

- Is prospectively planned
- Has valid statistical approaches on modification of design elements that have α-control (ICH E-9)
- Has valid point estimate and CI estimates
- Utility of drawing strength from external trials, but, not too much
- Careful use of "learning phase" in "confirming" phase
- Has SOP/infrastructure/firewalls on adaptive process monitoring – bias issue & trial integrity
- Has SOP/logistics on *adaptive design decision*
- Includes documentation of actual monitoring process, extent of compliance, potential impact on study results

Trial Logistics Models Seen So Far

Principle – Independence and objectivity

Independence

Objectivity

- Sponsor-Only Internal Model: blinded ⇐ ⇒ unblinded
- ISAC Model: ISAC (blinded ⇐ ⇒ unblinded) ⇐ ⇒ Sponsor
- DMC-Only Model: DMC ⇐ ⇒ Sponsor
- Combination Model: ISAC ⇐ DMC ⇐ ⇒ Sponsor
  ISAC ⇐ Sponsor

➔ *Relevance to Multi-Regional Clinical Trials*

➔ *Legal consequence of confidentiality agreement ?*

➔ *Need more experiences and some proposals !*

Not All Trials Need DMC

- Will establishment of DMC enhance the safety of trial participants? DMC useful when
  - Interim results are highly favorable, unfavorable or futile that might ethically require early study termination
  - A priori reasons of particular safety concerns
  - Possibility of serious toxicity from prior information
  - Study is performed in potentially fragile population, at elevated risk of death or other serious outcomes
  - Study is large, of long duration, and multi-center
- Is DMC review practical, e.g., short trial ?
- Will DMC help assure scientific validity of the trial, e.g., compelling external new info ? **Distinguishing point to AD**

* FDA DMC Guidance, 2006

Industry-Sponsored Clinical Trials

Academic Governance: 2 General Approaches

I. Steering committee (SC) is composed of academic investigators and has full access to all of the study data and reports

II. Steering committee is appointed by the company, but, the clinical trial database is exclusively controlled by the company and "access" provided to the investigators – the authors of SCs can send queries to the company, but, the SC does not have a copy of the database and no outside statistician has independent access to the raw data – consequently, the ability, the extent, and depth of external statistical confirmation may not be exploitable

- Call for true independent outside statistical confirmation (doable with approach I) of trial results to improve the quality of reporting

Some Examples on Trial Integrity Issue

- Clinical Investigators (medical researchers)
- Drug Sponsor
- Physicians and/or patients
- DMC

Potential Operational Bias

Medical Researchers Violate Confidentiality Agreement

- Seattle Times investigation (August 7, 2005)
  - Found at least 26 cases in which doctors have leaked confidential and critical details of their ongoing drug research to Wall Street firms
- Doctors signed confidentiality agreements to keep research secrets until company announces the results, but, violated
- Can introduce bias into drug trials
- Possibly halt developing of potential life-saving drugs

Potential Operational Bias
Unblinding of Ongoing Group Sequential Trial

- Available documents showed that the sponsor actually unblinded the ongoing study (RECORD) 2 weeks earlier, but, made belief it was actually physician-scientists' (SC) decision (not the sponsor) to unblind the study and publish the interim results
- Status quo: scientific leak of 'manuscripts under review' (meta analysis of 42 RCTs a showing of increased CV risk) to sponsor, prompted dialogues at the highest level, extensive analyses by sponsor statisticians and concluded: THERE IS NO STATISTICAL REASON FOR DISREGARDING THE FINDINGS AS PRESENTED

Potential Operational Bias
Interpretability Issues of Study Results

- RECORD : Open-Label Non-Inferiority GS Safety Trial, δ_{NI} **= 1.20**
- Sponsor's decision to unblind ongoing study to ➔ **Integrity of trial data in an open label NI study?** This extremely unusual procedure can seriously undermine statistical validity & credibility of final trial results;

1^0 : CV hospitalization or CV death

	CNTL (n=2220)	TRT (n=2227)	HR (95%CI
Interim results (1^0)	267	243	1.11 (0.93, 1.32)
Final results (1^0)	321	323	0.99 (0.85, 1.16)
CV death (interim)	29	35	0.83 (0.51, 1.36)
CV death (final)	60	71	0.84 (0.59, 1.18)
Heart Failure (interim)	47	22	2.15 (1.30, 3.57)
Heart Failure (final)	61	29	2.10 (1.10, 4.10)

Potential Operational Bias
Patient Psychology Rather Than Unblinding) ?

- Trial #1 appears to suggest subset effect (not prospectively specified after unblinded final analysis (prev. ~60%); ITT failed !
- Trial #2 near accrual completion (based on Trial #1 exploratory finding) amended protocol and SAP to ADAPT (no interim look)

  (1) change 1^0 analysis to subset; (2) increase 100 pts for subset (why) (observed prev. ~ 65%)

	CNTL (N~130)	TRT (N~125)	p-val
% data prior to change	<3/4	2/3	
Success Rate (pre)	55%	70%	.038
Success Rate (post)	71%	76%	.680
#1 post-hoc subset	57% (55%)	72% (65%)	.038(.161)

Potential Operational Bias
Quality and Credential of DMC

- DMC Charter & DMC SAP developed only after 1st DMC meeting and provided ~ half year after trial initiation and 3 days prior to 2nd DMC meeting (planned interim analysis; 1^0: 1yr event endpoint)
- One interim at about 50% completed 3-month treatment for efficacy or futility or for sample size re-estimation with no detail on the procedure other than to say based on blinded review
- At 2nd DMC meeting after planned interim, DMC recommended (i) to continue enrolling only +ve subset (stratification); (ii) to perform one additional interim analysis on +ve subset in 3wks
- Little data on 1^0 endpoint at 2nd DMC; seek regulatory buy-in by showing unblinded interim results → **where are firewalls ?**
- **Independence** DMC ←→ ISAC (blind and unblind teams) **unclear**

Beyond fixed design - patients, investigators don't need to know

How much details should be described in patient consent form or investigator participation form?

- whether sample size is increased
- What particular (adaptive) randomization method is used
- Which treatment arm is dropped (or added)
- Whether the study objective has modified
  - S to NI or NI to S; Targeted or untargeted population, etc.
- Whether the primary endpoint has changed
- What the statistical decision rule is
- Whether the study is a Ph II or Ph III or (seamless) combination
- …….

* Wang SJ, SCT 2006

Beyond fixed design – what do patients/investigators need to know

- The design to the extent the specific new treatments to be randomized, but, blinded to which treatment patients would receive
- Patient consent form in general term
- Investigator participation form in general term
- Investigators' role in CRF
- Standard Operating Procedures on those needing to "inform investigators & patients" described in the "trial conduct logistics"

* Wang SJ, SCT 2006

Follow-up on Real-Time Inspection*

Can We Build and Improve from Existing System?

* Ball L, Adaptive Design Guidance Workshop, 2010

Clinical Research Assistant (CRA)

- Sponsor may use CRO for clinical site monitoring
- The CRA from CRO does real time monitoring to check and correct the problem if investigators do not follow the SOP – little to no professional authoritative act
- Sponsor may use another CRO for database management
- There should be a flow chart describing the logistics of the interaction models among all involved parties
- CRA monitors according to the flow chart
  - The timing of each task; paper trails to confirm the timing
  - Follow the instruction: how was the task got done – firewall ?
  - Outcome of the task: was it done as expected?

Raise Quality of External CRA Real-Time Monitoring to Real-Time Inspection

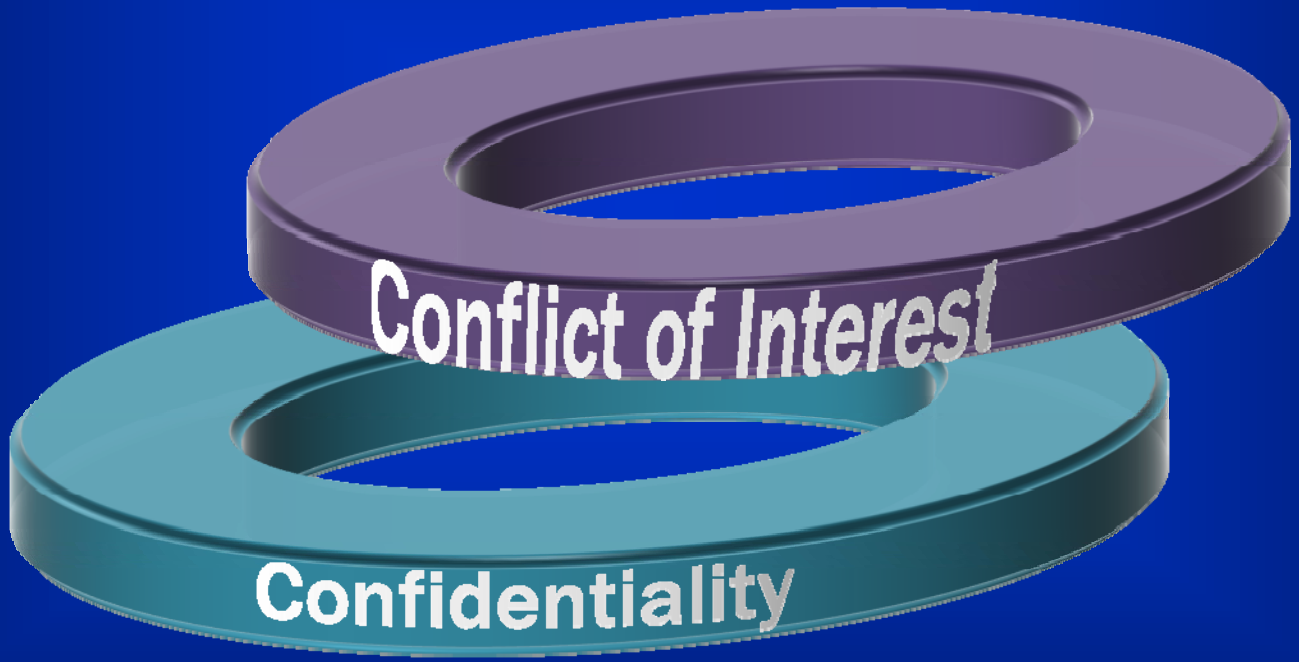
- Professional authority and qualification of CRA, e.g., associate
- Role and increased responsibility of CRA from CRO
- Does real-time monitoring to correct the problem require knowledge of treatment code?
- Real-time inspection should not need knowledge of treatment code
- Quality system including procedures and processes for establishment of firewalls for data quality and confirmation of trial integrity

Information flow needs to be controlled in a clinical trial with an adaptive design to avoid

- known or guessed results from a first stage impact on the results seen in later stages of a trial and introduce systematic bias
- the estimate of the treatment effect and the overall results of a trial un-interpretable
- post-hoc discussions about what constitutes an appropriate procedure for design modifications, or a systematic difference between results found in different stages

➔ Need due consideration at planning stage

Key Components for a Successful Adaptive Trial



Monitoring or Decision Making for Adaptive Design Purpose

- An infrastructure allowing for monitoring adaptive trial conduct

Standard Operating Procedures

- Charters of all parties including responsibilities and ensuring compliances
- Formats of meetings and adaptive interim reports
- Similar to DMC, integrity of trial conduct while maintaining independence

Establishment of Firewalls

- Who will monitor
- What to monitor
- Record the monitor process
- Describe how firewalls so established ensure no biased implementation of the trial
- What are consequences without follow SOP?
- Ensure result interpretability

Concluding Remarks

- To balance the innovative approaches by adaptive design clinical trials with the need to ensure trial integrity, conventional on-site inspection may be acceptable if there is trust in the system
- Trust factor of trial integrity will rely on accumulating experiences using different trial logistics models
- It may be expected of a quality system to confirm trial integrity if sponsor builds on and raises credibility of real-time inspection for adaptive trial implementation
- Independence and objectivity of such system may require a committee similar to DMC, but, separate from DMC