Session #18

DSMB Roles in Adaptive Design Trials: Regulatory Experiences & New Challenges

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* Professional views expressed are those of the authors and not necessarily those of U.S. FDA
Acknowledgments

FDA/CDER Review Teams/Divisions/Offices Coordinated Efforts with Office of Biostatistics

Guidance for Clinical Trial Sponsors:
Establishment and operation of clinical trial data monitoring committees

Educational Efforts via Case Sharing
Scientific vs Regulatory Review Recommendations

Wang, Hung, O’Neill (2011, European Neuropsychopharmacology Journal 21:159-166)
Over-arching principles

“The well-being of trial participants takes precedence over societal interests” – The World Medical Association Declaration of Helsinki
Key components for a successful Adaptive Design Trial
Guidance for Clinical Trial Sponsors: Establishment & Operation of Clinical Trial Data Monitoring Committees

- Became available March 2006 – time to revisit
- Started IND submissions on newer adaptive designs – guidance not address newer adaptive DMC monitoring
- Discussed firewalls & protection of interim results
- Discussed interactions with FDA vs FDA role in a GSD
- Discussed multiple models for independent statistician
Monitoring with an Adaptive Design

- Interim unblinding
  - Beyond group sequential design
  - Desired sponsor’s engagement
  - Frequent (rule driven) vs defined timing for unblinding

- Different levels of concerns
  - Exploratory (learning trials)
  - Confirmatory (registration trials)
  - Seamless phase 2/3
    - Design characteristics: learn or confirm
    - Confusing?
Clinical Trial Committees

- Steering Committee
- Sponsor
  - siDMC
  - IRC vs SC
  - Senior management designee
- ISAC
- IDMC, DSMB, DMC
- ......
- Data management
Firewalls

DMC

Regulator

Sponsor
IRC

ISAC

Safety

Integrity

Efficiency
DMC responsibilities

Before Adaptive Designs
- Study enrollment
- Data quality
- Patient safety

Recommendations on conduct of clinical trials, trial monitoring
Membership, Documentation, Process, Implementation
Open vs closed meeting

With Adaptive Designs
Expanding scopes to include
- Recommendation on design changes of a ongoing trial?

Q: Can still meet expectation on
(i) Maintain ‘independence’ & avoid conflicts of interests?
(ii) Confidentiality?
(iii) Trial integrity

Uncharted and evolving!
Sponsor Only Internal (SOI) Model

Unblinded Statistician

Blinded Statistician

Drug Sponsor

IRC

Regulatory Agency

FDA
EMA
PMDA
...

Trust

Firewalls

Unblinded party: Stat to perform IA following adaptation rules; Internal Review Committee (IRC) to make AD decision

Blind regulator & maintain blind for in process control of an ongoing trial

Wang SJ, HSPH - Merck May, 2011

Wang SJ, SCT May-2012
Independent Statistics Analysis Center (ISAC) Model

- Drug Sponsor
- ISAC
- Unblinded Statistician
- Blinded Statistician
- IRC
- Decision

Regulatory Agency
- FDA
- EMA
- PMDA
- ...

AD Recommendation

Wang SJ, HSPH-Merck May, 2011
Data Monitoring Committee (DMC) Model

- Drug Sponsor
- Blinded Statistician
- DMC
- Clinical Experts
- Statistical expert (Ethicist)
- IRB
- FDA
- EMA
- PMDA
- AD Recommendation
- Decision
- Regulatory Agency
- ISAC
- Unblinded Statistician

- Drug Sponsor
- DMC
- Clinical Experts
- Statistical expert (Ethicist)
- IRB
- FDA
- EMA
- PMDA
- AD Recommendation
- Decision
- Regulatory Agency
- ISAC
- Unblinded Statistician

Wang SJ, HSPH-May, 2011
Academic Governance Models

- SC includes academic investigators having full access to all of the trial data and reports
- SC appointed by drug company; trial data is exclusively controlled by company and ‘access’ provided to investigators
  - Authors can send query to company
  - SC doesn’t have a copy of trial data
  - No outside statistician has independent access to raw data
  - Uncertain on “extent and depth” of statistical confirmation

Nissen SE 2010
Combination Model

DMC
Clinical Experts
Statistical expert (Ethicist)

ISAC
Unblinded Statistician
Blinded Statistician

Drug Sponsor
Blinded Statistician

IRC
Decision
AD Recommendation

Regulatory Agency
FDA
EMA
PMDA
...

Wang SJ, HSPH-Merck May, 2011
## Adaptive Monitoring Logistics Models

### When without a DMC
- **Formal DMC not required**
- **If Sponsor-Only-Internal Model**
  - Confidentiality agreement: legal consequence ???
- **If ISAC Model**
  - Firewalls within ISAC
  - Rely on professional ethics!
- **Sponsor’s decision to adapt**

### When with a DMC
- **Safety Monitoring needed**
- **If DMC Model**
  - Discretion (can overwrite)!
  - Objectivity of ‘safety’ ?
  - Tend to follow adaptive rule?
- **If Combination Model**
  - Separate roles of adaptation recommendation from safety monitoring
  - Who should make adaptive recommendation ???
  - Sponsor’s decision to adapt
Modified Combination Model for A&WC Adaptive Trial

- DMC (Clinical Experts, Statistical experts, Ethicist)
- ISAC (Qualified Statistician)
- AD Recommendation
- Decision
- Drug Sponsor
  - SAP but no IA details
- Regulatory Agency (FDA, EMA, PMDA, ...)

Wang SJ, HSPH-Merck May, 2011
Good Adaptive Monitoring Practice

Roles of ISAC(s):
- Blinded Adaptive
- Unblinded Adaptive
- IAP Only (No SAP)

Roles of DMC when required:
- Safety Monitoring
- Provided with Emerging Data

Roles of Sponsor:
- Responsible for Adaptive Decision

Role of SC:
- Depends on committee composition

Roles of Regulator:
- Public Health

- Those Needing More Inputs/Debates/Discussions/Experiences
- Who should make Adaptive Recommendation?
- Who should enforce Confidentiality Agreements?
- Separate IAP vs SAP and only ISAC or DMC sees IAP?
Concluding Remarks

- From well-understood GSD to less well-understood AD
- CRO and related organizations – a growing industry that collect, clean and analyze data, unblinded role and provide summary (semi) unblinded data to DMC’s
- Is there a need of a new models for governance and trial decision making as such the integrity of the trial is maintained and efficiency is improved so as to streamline AD clinical trial and build quality into it simultaneously?
- An objective of the Clinical Trials Transformation Initiative