DIA ADSWG Best Practice Subteam Update

August 12, 2015

Co-Chairs: Weili He, Eva Miller
Team Charter: ADSWG BP Subteam
Weili He (Co-Chair)/Eva Miller (Co-Chair):

**Background**

- In the past decades, there have been many articles that addressed critical AD trial design and statistical methodological issues.
- However, to date, the use of AD trials in clinical development is still not wide spread.

**Current Status**

- We have formed the Best Practices Subteam (BPST) core team
- We have recently formed two workstreams:
  - WS#1: Knowledge and accessibility to software
  - WS#2: AD Trial Characterization and best practice sharing

**BPST Objectives**

- Promote greater use of AD trials in clinical development across industry and greater acceptance of AD trials by regulatory agencies by
  - Clarifying the myths and concerns which dissuade use of AD within clinical trials
  - Focus on perceived barriers to implementation of ADs and help lift the barriers
  - Identifying gaps in implementation
  - Promoting increased communications with regulatory agencies and transparency in the conduct of AD trials
  - Gaining further clarity on what is meant by “less well understood AD designs” and how to get them to “more well accepted AD designs” if they are implemented correctly
  - Learning when the draft guidance will be finalized and what will change
  - Sharing case studies and lessons learned
  - Identify and publicize AD Best Practices
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**BPST Deliverables**
- Organize workshops/conferences with representatives from various disciplines including regulatory agencies to share the Subteam finding and gain understanding and consensus
- Publish white paper(s) on BPST findings

**BPST Membership**
- Currently we have the following members:
  - Weili He (WS#2 Co-lead), Merck & Co., Inc.
  - Eva Miller (WS#1 Co-lead), inVentiv Health clinical, Inc.
  - Vladimir Dragalin (WS#1 Co-lead), J&J
  - Paul Gallo (WS#2 Co-lead), Novartis
  - Ken Getz, Tufts University School of Medicine
  - Yannis Jemiai, Cytel Inc.
  - Qi Jiang, Amgen
  - Lisa Kammerman, Astra Zeneca
  - Ken Koury, Merck & Co., Inc.
  - Xuefeng Li, CDRH, FDA
  - Annie Lin, CBER, FDA
  - Jeff Maca, Quintiles
  - David Moriarty, J&J
  - Kristin Neff, Invivo
  - Tom Parke, Tessella
  - Marc Walton, J&J
  - Cunshan Wang, Pfizer
  - Sue-Jane Wang, CDER, FDA
  - Katherine Woo, J&J

**BPST Structure**
- ~15 members from various industry and regulatory agencies with experience in AD trial implementation
- Members from various different disciplines (statisticians, clinicians, clinical operations, clinical supply management, project management) and pharmaceutical companies, CRO, ARO, or regulatory agencies
- May add additional members as needed
Ongoing Work with
WS#1: Knowledge and accessibility to software

Co-Leads: Eva Miller, Vlad Dragalin
DIA ADSWG BP Subteam WS#1 Membership

- Eva Miller, Inventiv Health clinical (Co-Lead)
- Vladimir Dragalin, J&J (Co-Lead)
- Aijun Gao, inVentiv Health clinical
- Weili He, Merck & Co., Inc.
- Yannis Jemiai, Cytel Inc.
- Jeff Maca, Quintiles
- David Moriarty, J&J
- Tom Parke, Tessella
- Katherine Woo, J&J
Knowledge and accessibility to software has been identified as a barrier to use of ADs.

To help lift the barrier, this work stream will survey available software (free, open-source, and commercial software) for use in:

- Protocol development, simulation, and analysis
- Adaptive design implementation

Software for protocol development and simulation cover adaptive designs from First in Man (CRM, EWOC) through Phase IV studies.

Software for implementation cover

- Platforms that handle firewalls (role based access) and audit trails (records of who had what access to what information when)
- Trial Enrollment
- Randomization/IVRS
- Drug Supply Management
Software characteristics

- Software characteristics to be covered include, but may not be limited to:
  - Descriptions of what they do
  - What kind of adaptive designs are included
  - Graphing capabilities
  - Level of documentation
  - Level of user friendliness
  - Ease of use
  - Required User level of statistical and software usage experience
The workstream has determined that software is needed at the following points of clinical trial development in both exploratory and confirmatory trials:

- Planning and simulations for:
  - Enrollment and/or event forecasting
  - Forecasting drug supply management
  - Sample size estimation/determination

- Implementation and analysis
  - Managing enrollment, randomization and drug supply
  - Ensuring data integrity and security
DIA ADSWG BP Subteam WS#1 Next Steps

- Develop a paper, including specific examples of what is available, what is best for specific situations and what is required for appropriate use of the software.

- The paper should be impartial and informative and serves as a point of reference to facilitate broader appropriate use of Adaptive Trial Designs within clinical research. The paper will probably take the form of a large table with some ancillary text.

- Develop presentations to communicate the information to various audiences and make the information more accessible.
Ongoing Work with
WS#2: AD Trial Characterization
and Best Practice Sharing

Co-Leads: Weili He, Paul Gallo
DIA ADSWG BP Subteam WS#2 Objectives

- Understand AD trials that are categorized as “Less well-understood”, with regard to specific features or aspects of those trials that may have led them to be categorized in that way.

- Review these features in regard to design and/or the end-to-end trial execution processes, and identify areas where suggestions and/or improvements may help in their acceptance.

- Study a collection of case studies on lessons learned

- Brainstorm on design improvements and share operational practices (by WS members), and develop best practices
DIA ADSWG BP Subteam WS#2 Membership

- Weili He (Co-Lead), Merck & Co., Inc.
- Paul Gallo (Co-Lead), Novartis
- Vladimir Dragalin, J&J
- Ken Getz, Tufts University School of Medicine
- Yannis Jemiai, Cytel Inc.
- Qi Jiang, Amgen
- Lisa Kammerman, Astra Zeneca
- Ken Koury, Merck & Co., Inc.
- Xuefeng Li, CDRH, FDA
- Annie Lin, CBER, FDA
- Jeff Maca, Quintiles
- Eva Miller, Inventivhealth
- David Moriarty, J&J
- Kristin Neff, Invivo
- Cunshan Wang, Pfizer
- Sue-Jane Wang, CDER, FDA
- Marc Walton, J&J
- Katherine Woo, J&J
FDA AD Guidance on “Less Well-Understood” Trials

- FDA draft AD guidance “Less Well-Understood” trial categories:
  - Adaptations for Dose Selection Studies
  - Adaptive Randomization Based on Relative Treatment Group Responses
  - Adaptation of Sample Size Based on Interim Effect Size Estimates
  - Adaptation of Patient Population Based on Treatment Effect Estimates
  - Adaptation for Endpoint Selection Based on Interim Estimate of Treatment Effect
  - Adaptation of Multiple-Study Design Features in a Single Study
  - Adaptations in Non-Inferiority Studies
Set of common opportunities and lessons learned in trial design or execution for these AD trials*

- Type I error control
- DMC review process: Internal vs. external DMC?
- Who are the decision makers? DMC members or sponsor? Can Sponsors trust DMC members making a business decision for the sponsor?
- Potential for subject heterogeneity across stages
- Potential and concerns for interim results being different from final results
- Potential for making decisions based on highly variable and may often be ambiguous results at IA
- Potential for mistakes in analysis or in study conduct that may not be discovered until final study stage
- Potential for overrun of subjects being recruited and what treatment groups the overrun subjects should be assigned too

* Various examples of these challenges will be elucidated based on different AD type
Collection of Case Studies

- We have collected study design and/or conduct details on the following trials:
  - ADVENT trial
  - LOTS trial
  - Sunesis VALOR trial
  - Raptor’s PROCYSBI
  - A Phase II/III Merck vaccine trial
  - INHANCE trial
  - A Population Enrichment Design Case Study
  - A Phase II/III seamless adaptive confirmatory trial with interim treatment selection - infants with proliferating hemangioma
  - Adaptive Treatment Selection Design
  - A-HeFT Trial
2015 Conferences - Sessions on adaptive designs by BP Subteam members:

- DIA Annual meeting
- ICSA/Graybill
- July 2015 KOL lecture series
- JSM
- FDA Industry/Statistics workshop
- DIA Annual Canadian Meeting
DIA ADSWG BP Subteam WS#2 Current Status (Cont’d)

- Develop two papers
  - A paper characterizing trial features of “Less Well-Understood” trials, describing the common and specific challenges with these trials, and providing thoughts and guidance with case study examples
    - Work in progress on this manuscript, target to have a complete draft by the end of Aug. 2015 and target to have a final manuscript by Oct. 2015
  - A paper on the collection of case studies, describing more details and summarizing best practices
    - Work in progress on this manuscript, target to have a complete draft by the end of Aug. 2015 and target to have a final manuscript by Oct. 2015

- Plan to submit two companion papers to the same journal together (DIA Journal: Therapeutic Innovation & Regulatory Science)
Plan for the next steps with the BP subteam

- After the completion of the first stage of work with various presentations and one manuscript from WS#1 and two manuscripts from WS#2, the subteam plans to develop additional areas of focuses to continue the work.

- Would appreciate input from ADSWG on the focus in the next stage