DIA Small Populations Workstream: Update 7-15

Cong Chen, PhD, Merck Research Laboratories
Robert A. Beckman, MD, Georgetown University
Agenda

• Mission
• Membership and organization
• Working subgroups
• Updates on working subgroups
• Presentations at upcoming DIA meetings
Mission

The group studies clinical trial designs, analysis methodologies, and development strategies relevant to small populations with emphasis on proof of concept and registrational studies. Small populations include those corresponding to rare diseases, but also biomarker-defined subgroups of common diseases, especially cancer. The group draws on its broad international membership across health authorities, industry, and academics and attempts to invent new approaches of potentially broad applicability, with a reasonable chance of health authority acceptance. These approaches will be shared with the community via publication and public presentations.
Membership

• 39 members as of 6-24-15
• Health authority leaders: 7
  – 2 EMA, 5 FDA (1 CDRH)
  – Opinions of health authority leaders are their personal views and do not represent official views of health authorities
• Large pharma: 15 (one also counted in academics)
• Biotech: 8
• Academics: 9
• Independent consultant (former FDA): 1
• 36 statisticians, 3 clinicians
• We welcome new members
• New members may join existing subgroups
Ohad Amit (GSK): Ohad.Amit@gsk.com
Zoran Antonijevic (Cytel): Zoran.Antonijevic@cytel.com
Bob Beckman (Georgetown, UCSF, Co-chair): eniac1915@gmail.com
Carl Fredrik Burman (AZ/Chalmers) Carl-Fredrik.Burman@astrazeneca.com
Cong Chen (Merck, Co-chair): cong_chen@merck.com
Yinpu Chen (Biomarin): YiChen@bmrn.com
Christine Gause (Merck): christine_gause@merck.com
Balarama Gundapaneni (Pfizer): Balarama.Gundapaneni@Pfizer.com
Li He (Merck) Li.He@merck.com
Yi He (CellDex): yihe@celldex.com
Chris Jennison (Bath): C.Jennison@bath.ac.uk
Sebastian Jobjörnsson (Chalmers): jobjorns@chalmers.se
Bertil Jonsson (CHMP): Bertil.Jonsson@mpa.se
Franz Koenig (Med Univ Vienna): franz.koenig@meduniwien.ac.at
Tony Koutsoukos (Ultragenyx) TKoutsoukos@ultragenyx.com
Glen Laird (Sanofi): Glen.Laird@sanofi.com
Lingyun Liu (Cytel): Lingyun.Liu@cytel.com
Membership list (II)

- Sandeep Menon (Pfizer): Sandeep.M.Menon@pfizer.com
- Cyrus Mehta (Cytel): mehta@cytel.com
- Robert O’Neill (Office of Biostatistics/Office of Translational Sciences, CDER, FDA): Robert.ONEill@fda.hhs.gov
- Lei Pang (Merck): Lei.Pang@merck.com
- Reena Philip (CDRH, FDA): Reena.Philip@fda.hhs.gov
- Francesco Pignatti (EMA): Francesco.Pignatti@ema.europa.eu
- Martin Posch (University of Vienna): Martin.Posch@meduniwien.ac.at
- Nusrat Rabbee (Berkeley): nrabbee@yahoo.com
- Mary Redman (Fred Hutchinson Cancer Center): Redman, Mary Wmredman@fredhutch.org
- Satrajit.Roychoudhury (Novartis): satrajit.roychoudhury@novartis.com
- Jeff Schwartz (Pfizer): jeffrey.h.schwartz@pfizer.com
- Tong Shen (Mallinkrodt): tt.0724@gmail.com
- Yue Shentu (Merck): yue_shentu@merck.com
- Rajeshwari Sridhara (CDER, FDA): rajeshwari.sridhara@fda.hhs.gov
- Ming Tan: Ming.Tan@georgetown.edu
- Shenghui Tang (CDER, FDA): shenghui.tang@fda.hhs.gov
- Marc Walton (JNJ): Marc Walton (mwalton9@its.jnj.com) (mwalton9@its.jnj.com)
- Sue Jane Wang (Office of Biostatistics/Office of Translational Sciences, CDER, FDA): suejane.wang@fda.hhs.gov
Membership list (III)

- Grant Williams (Williams Cancer Drug Consulting LLC; former FDA, Novartis, GSK): grant@wmscancerdrugs.com
- Min Yao (Amicusrx) myao@amicusrx.com
- Sammy Yuan (Merck): Sammy.Yuan@merck.com
- Joey Zhou (Ultragenyx): yzhou@ultragenyx.com
Organizational

• Monthly TC for full workstream membership
• Working subgroups meeting by TC monthly or as needed
• Membership may be at various levels of contribution
• All members are given the opportunity to review and comment on draft publications from all the working subgroups
Working Subgroups

• Nature and Extent of Evidence Needed for Approval in Rare Diseases (co-chairs: Jeff Schwartz, Pfizer; Joey Zhou, Ultragenyx)
• Predictive Subgroup Methodologies (chair: Carl-Fredrik Burman, Astra Zeneca/Chalmers)
• Adaptive alpha allocation (chair: Cong Chen, Merck)
• Pathway study designs (chair: Cong Chen, Merck)
• Master protocols (co-chairs: Ohad Amit, GSK; Mary Redman, Fred Hutchinson Cancer Research Center)
Nature and Extent of Evidence Needed for Decision (NEED) (Schwartz/Zhou)

• Leader: Jeff Schwartz/Joey Zhou
• Core Contributors: Balarama Gundapaneni, Sebastian Jobjornnson, Francesco Pignatti, Zoran Antonijevic, Bob Beckman
• Contributors: Chris Jennison, Franz Koenig, Cyrus Mehta, Bob O’Neill
Background

• Small populations/rare disease present unique and significant challenges
• Nature and extent of evidence may not be able to reach the same threshold of substantiability usually expected and required
The Problem

• There is a **delicate balance** between the **need for valid and persuasive evidence** and the **need for flexibility** in the constrained setting of rare disease.

• There “is a **fine line** between such flexibility and potentially approving unsafe drugs for use.”
The Questions

• What can be done to help drug developers provide suitable evidence for regulators to reach positive decisions?
• What methods of evaluation can be developed to assist regulators in navigating the “fine line”? 
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<thead>
<tr>
<th>Broad Category</th>
<th>Specific terms</th>
<th>Comments</th>
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<tr>
<td>Limited information on natural history of disease</td>
<td>the natural history of rare diseases is often unclear</td>
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<td>relevant prognostic subgroups are often unknown</td>
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<td>incidence is often unknown/ incidence may rise when a therapy becomes available such that it is worthwhile to have the diagnosis</td>
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<td>Limited information on the underlying pathophysiology of the disease</td>
<td>Not understanding the underlying biology</td>
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<td>lack of knowledge in potential biomarkers (surrogate for primary endpoints) for pivotal study</td>
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<td>Limited research capability</td>
<td>Insufficient number of patients</td>
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<td>Unprecedented research</td>
<td>No standard therapy</td>
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<td>No precedent from earlier clinical development program</td>
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<td>Validation of clinical endpoints</td>
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<td>Difficult in claiming / identifying primary endpoints</td>
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Immediate Plans

• Currently focusing on review of cases of approved drugs in rare diseases
• Immediate goal is presentation at June DIA meeting
• Manuscript will be prepared based on review of cases
• A second research area and manuscript may be prepared with novel designs or approaches to address issue
Predictive Subgroup Methodologies (Burman)

• Leader: Carl-Fredrik Burman
• Primary contributor: Martin Posch
• Core contributors: Sebastian Jobjornsson, Franz Koenig, Thomas Ondra, Martin Posch, Nigel Stallard, Bob Beckman
• Contributors: Zoran Antonijevic, Chris Jennison, Olga Marchenko, Francesco Pignatti, Nusrat Rabbee, Jeffrey Schwartz, Tong Shen, Joey Zhou
Research Focus: Decision Analysis Focus for Design of Phase 3 Programs With Biomarker Subsets: Background

- Application of decision analysis to optimization of phase 3 programs
  - Chen and Beckman (Statistics in Biopharmaceutical Research, 1: 431-40, 2009), Beckman, Clark, Chen (Nature Reviews Drug Discovery, 10: 735-48, 2011):
  - Consideration of decision analysis with utility functions from different stakeholders
Current Effort

• More general utility functions that depend on cost explicitly as well as on effect sizes
• Expand consideration of stakeholders to include health authorities
• Derive decision rules that optimize expected utility subject to frequentist properties
  – Sponsors and health authorities may have different priors and utility functions
• Consider realistic prior distributions rather than point priors
• Methods oriented paper in development
• Applications oriented paper planned for future
Pathway design and alpha allocation working subgroups (Chen)

• Pathway design:
  – Leader: Cong Chen
  – Primary contributors: Cong Chen, Bob Beckman
  – Core contributors: Zoran Antonijevic, Joey Zhou
  – Contributors: Lingyun Liu, Christine Gause, Sammy Yuan, Sebastian Jobjornsson
  – Advisors: SueJane Wang, Rasika Kalamegham (AACR)

• Alpha allocation:
  – Leader: Cong Chen
  – Core contributors: Lei Pang, Bob Beckman, and Yue Shentu
  – Contributors: Carl-Fredrik Burman, Franz Koenig, Lingyun Liu, Lei Pang, Tong Shen, Joey Zhou
  – Advisor: Sue-Jane Wang
Update

• **Pathway**
  – Beckman RA, Antonijevic Z, Kalamegham R, Chen C. Design for a Phase 3 Basket Trial in Multiple Tumor Types Based on a Putative Predictive Biomarker. Submitted to CCR in 6/2015.
  – Chen C, et al. Statistical Design for a Prototype Phase 3 Basket Trial in Multiple Tumor Types Based on a Putative Predictive Biomarker. To be submitted.

• **Alpha allocation**
Multiplicity adjustment for a basket trial

• Suppose that the overall basket study consists of $k$ tumor cohorts of equal size
• An interim analysis is conducted at information time $t$ to prune non-performing cohorts
• Which alpha level (denoted $\alpha^*$) should the pooled analysis at the end be tested at to keep the overall Type I error rate under 2.5%?
An example when a small negative trend is used as criterion for pruning.
Informational design

• Oncology drug developers often decide to initiate Phase III randomized confirmatory trials at risk after preliminary anti-tumor activities are observed in small Phase I/II single arm studies.
  – Adjuvant studies are often initiated w/o any data
• The preliminary data can hardly provide the much-needed information for selecting a biomarker cutpoint or prioritizing a biomarker hypothesis for Phase III testing.
• The data seldom provides any insight on how the treatment benefit evolves over time.
Approaches

• Conventional adaptive-design that rely on interim analyses for modifying the study design are less reliable because the treatment effect observed at an interim analysis may not be the same as in the final analysis.
  – The use of an intermediate endpoint for interim decision makes it even more unreliable because the predictive value of an intermediate endpoint is often unknown for drugs with a new mechanism of action.

• We propose to add an analysis at end of the Phase III trial in a subgroup of patients representative of the overall study population to fine-tune the hypothesis testing strategy of the study (informational design).
Conventional interim analysis

Interim analysis with limited follow-up

Final analysis with complete follow-up

Patients ordered by accrual
Informational analysis vs interim analysis

Patients selected for informational analysis

Interim analysis with limited follow-up

Final analysis with complete follow-up
Informational design vs seamless design

Data used for adaptation in seamless Ph II/III design

Data used for adaptation in informational Ph III design
Master Protocol Subgroup (just formed; Amit/Redman)

• Co-chairs: Ohad Amit, Mary Redman
• Core contributors: Martin Posch, Sammy Yuan, Bob Beckman
• Advisors: Reena Philip, Shenghui Tang, Rajeshwari Sridhara, Bob O’Neill
Presentations by Small Populations Workstream

• Members of the group have given presentations, workshops, or appeared on panels at:
  – DIA Annual Meeting, 2014
  – Trends and Innovations in Clinical Trial Statistics, 2014 (Quintiles, University of North Carolina)
  – Symposium on Small Populations, Medical University of Vienna, 2014
  – DIA/International Association for Bayesian Analysis Joint Adaptive Design and Bayesian Statistics Conference, 2015
  – Boston Oncology Summit
Presentations by Small Populations Workstream II

- Members of the group have given presentations, workshops, or appeared on panels at:
  - DIA 2015:
    - Workshop 1: Rare Diseases and Subgroups Defined by Tumor Evolution: Common Themes and Challenges (Schwartz, Beckman, Grant Williams (former FDA)
    - Workshop 2: Predictive Subgroup Analyses and Molecular Basket Designs (Burman, Sridhara, Beckman)
Presentations by Small Populations Workstream: Planned

- Two presentations at 2015 ASA Joint Statistical Meeting
- One short course at FDA/Industry Statistics Workshop and one at Deming Conference
- One invited presentation at FDA/Industry Statistics Workshop
- One invited presentation at BASS XXII
- Trends and Innovations in Clinical Trial Statistics, 2016: (Posch, Beckman on organizing committee; Posch, Chen, Beckman confirmed speakers)