Designing Generalizable Trials: Why Inclusivity Matters

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Disclaimer

• The thoughts expressed are my own and should not be construed to be FDA policy.
• Having worked on 1) drugs, biologics, devices 2) therapeutics and diagnostics: I think inclusivity always matters.
Outline

• Background
• Design and Analysis
• Confounding
• Diagnostics
• Meta-analyses
• Rethinking our approaches
• Conclusions
Background

Examples where demographics matter:

Medical products:
CV disease; Diabetes; Cancer,…

Factor 8 safety (Hemophiliacs)

Unrealistic to assume we will have separate trials for each group routinely.

How to pick and choose when it matters?
Representativeness

• Randomization in bigger studies will lead to balance among the treatment groups
• No guarantees: represent the intended population of interest enough patients to characterize all subgroups of interest.
Interaction Hypotheses

- Interaction effects: treatment by subgroups
  Low power
- Sex by treatment: some power (50:50?)
- Race by treatment: almost no power
- Power: goes down with more groups; fraction of each in the study: 50:50 is best if 2 groups
Qualitative vs Quantitative Interactions

• **Quantitative**: Treatment effect varies by sex but always same direction: Treatment better than control in all groups

• **Qualitative**: Treatment works for some but not others. Effect: positive for one group, zero or negative for other group

• FDA: qualitative interactions of concern
Designing with Diversity in Mind

• Stratification
  Balancing: sex and race etc among arms

• Inclusivity: Why not have men in breast cancer trials?

• Do we need some groups overrepresented? How to analyze?

• Options: weighting; ANCOVA; ….
Confounding: Demographics

- Sex and body size
  - Device implants
  - Dose in a pill
- Sex and compliance in a drug trial (?)
- Dark Skin and Ethnicity
- Sex and age (inclusion/exclusion criteria?)
- Be sure you can interpret the results!
Confounding: Clinical sites

• Devices & Surgical Skill
  Big Center, Small Center
• Oncology & surgery before adjuvant therapy
• Don’t confound ethnicity and surgical skill
• Multiregional trials:
  Sometimes different standard of care
  Genetic differences (eg HLA variants)
  Ethnicity: definitions needed in advance
Diagnostics & Demographics

• Reference Intervals
• Comparing quantitative measures
  Analytical range
• Cutoffs for qualitative results
• Genetic markers including HLA
• Predictions of risk in ethnic groups
Meta-analyses

• Consistency of definitions
  Clinical endpoints (PROs?, CV endpoints)
  Ethnicity or Race
  …may vary if US or multi-regional

• If studies under-enroll minorities, meta-analyses will not fix all.

• Inclusion/exclusion criteria can vary

• Control arm may vary among studies

• Usual issues: publication biases
Rethinking our approaches

• At FDA
  Epidemiologists focus on drug safety
  …particularly in postmarket
• More help at planning stages:
  Demographics of disease/therapeutic area
  Knowledge of differences in groups
  Multi-regional studies are here to stay
Some conclusions

• As we seek precision medicine:
  Demographics in our trials will matter
  Understanding basis for observed differences in product performance will inform clinical practice.
FDA Guidances

- Final Guidance for Industry and FDA Staff: Evaluation of Sex-Specific Data in Medical Device Clinical Studies. August 2014
- Draft Guidance for Industry and FDA Staff: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices April 2015
- Food and Drug Administration, FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data 2014
Other references


• ICH E17: General principle on planning/designing Multi-Regional Clinical Trials (Concept Paper)