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

- M. Alosh, K. Fritsch, M. Huque, K. Mahjoob, G. Pennello, M. Rothmann, E. Russek-Cohen, F. Smith, S. Wilson, L. Yue (2015) Statistical Considerations on Subgroup Analysis in Clinical Trials. Statistics in Biopharmaceutical Research (On-line)
- ICH E17: General principle on planning/designing Multi-Regional Clinical Trials (Concept Paper)