Heterogeneity of Treatment Effects in Clinical Trials*

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*This presentation reflects the views of the author and should not be construed to represent the views or policies of the U.S. Food and Drug Administration

Some topics discussed

- Subgroup identification; Finding the right subgroup

- Benefiting subgroup confidence subgroup

  - Sometimes (always) those are the types of conclusions that we that can actually be drawn from data, once we accept that treatment effects vary across patients and average treatment effects vary across subgroups of factors

HEADLINES

- Treatment effects vary across individual patients
  - For given patient, treatment effect/difference is difference in outcomes if randomized to experimental group vs if randomized to control group
  - Baseline attributes, characteristics, condition, severity, genetics, etc. may affect the size of treatment effect/difference
- What we wish were tested vs. What we are actually testing
  - Actually testing: Average treatment effect is positive
- About more than preserving alpha when drawing conclusions
  - Pay attention to what is actually demonstrated

Not just approval decisions

- Can do better at informing patients of benefit-risk that apply to patients like them
  - characterize size of treatment effect with appropriate uncertainty

A traditional approach to clinical trials

- Homogeneous patient population to minimize variability of outcomes

- Unadjusted analysis used (no reason to adjust for imbalances)

- Assume treatment effects do not vary across subgroups (unless proven otherwise)
  - The overall estimated treatment effect applies to everyone

Clinical trials in diverse populations

- Enroll, randomize diverse patient population; follow all patients to the endpoint

- Account for prognostic factors in analysis

- Evaluate for heterogeneous treatment effects (HTE)

- Provide best information of treatment effects
  - for single factor, multi-factor, accounting for confounding

Non identical but related questions

- Question whether a product works in patients of subgroup A is not the same question as whether a product works in patients of subgroup B, but they may be related questions

- Size of relative cardiovascular risk reduction a product may depend on LVEF

How multiplicity applies for subgroups generally not understood after testing in overall population

- Positive average treatment effect demonstrated for overall population

- Both of two subgroups that partition overall population individually fail to demonstrate a positive treatment effect

- We know we have made at least one error

- Why are we assuming no treatment effect in all subgroups when we've already demonstrated positive average treatment effect for overall population

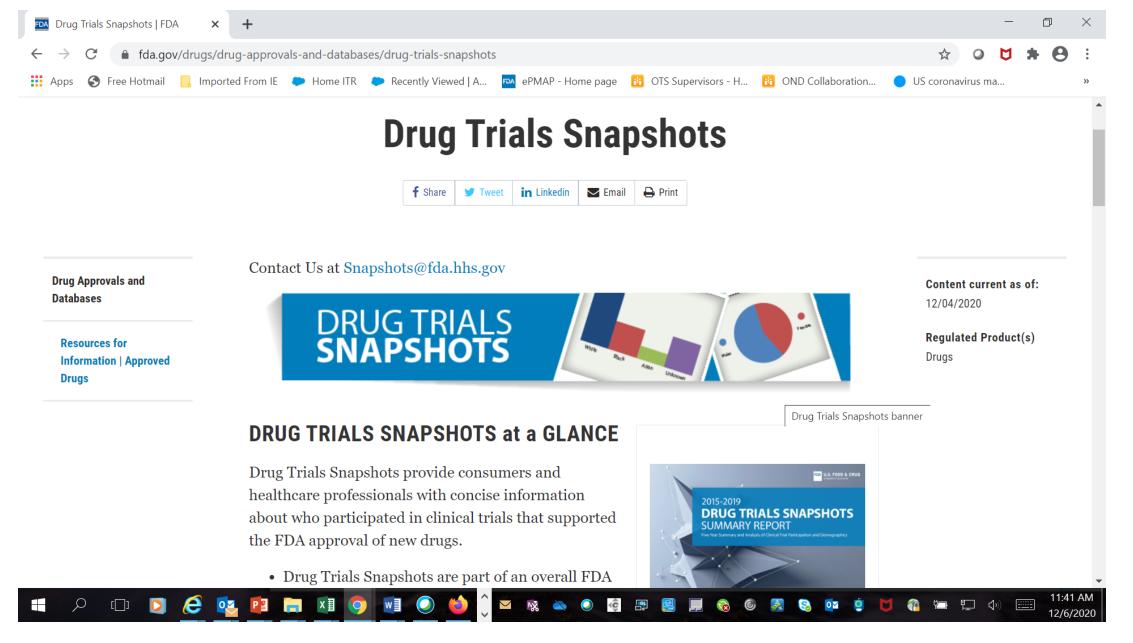# Overall results statistically significant

Given the overall result is statistically significant (favorable)

- For every subgroup of interest, the 95% CI rules out no difference in a favorable direction

  – Strong evidence there is an effect in all those subgroups

- For a given subgroup of interest, the 95% CI rules out no difference in a favorable direction

  – Strong evidence there is an effect in that subgroup

Claim vs. Individual treatment decision

- Atenolol or losartan for CV risk reduction in Black population
  - Are the results persuasive enough for a claim?
  - What about the persuasiveness on a treatment decision if the only choices to choose from were atenolol and losartan?

Impact Story

- FDA Impact Story (2019). Using innovative statistical approaches to provide the most reliable treatment outcomes information to patients and clinicians. Available at

using-innovative-statistical-approaches-provide-most-reliable-treatment-outcomes

Recent Symposiums and Workshops co-sponsored by FDA on Heterogeneous Treatment Effects

- Nov 28, 2018, Symposium of Assessing and Communicating Heterogeneity of Treatment Effects for Patient Subpopulations: Challenges and Opportunities
  - Agenda, Slides and Recording at https://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/news-and-events/Critical-Issues-in-Heterogeneity-of-Treatment-Effect.html

- Nov 30 - Dec 1, 2020, Workshop on Heterogeneity of Treatment Effects in Clinical Trials: Methods and Innovations
  - Agenda and Recording at https://mrctcenter.org/news-events/heterogeneity-of-treatment-effects-in-clinical-trials-methods-and-innovations/#1602863324215-1289c9d5-a82a

Some messages from the session

- We can do more or better at understanding heterogeneous treatment effects
- Have used shrinkage estimation for some drug trials snapshots
- More complicated/better models could include factors known to affect the treatment effect
- Doable (somewhere) in some settings to have a repository of data to be used to provide individual patient advice which can account for patient preferences, patient demographics and medical history

Some Topics/Questions of interest

- Representation in clinical trials

- What can a patient like me expect?

- If there is a benefit overall, where may there not be benefit?

- Difference in using subgroup analyses to make a claim vs. individual patient treatment decisions

- How do overall results affect how we view subgroup results?

- Is there consistency of treatment effect?