Statistical Approaches Under Heterogeneous Treatment Effects

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Outline

- Designing and analyzing clinical trials with diverse populations
- Heterogeneous Treatment Effects
- Drug Trials Snapshots
- FDA Impact Story
  - Relevancy of data outside the subgroup of interest
- Shrinkage Estimation and Example

Designing and analyzing clinical trials with diverse populations

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

Heterogeneous Treatment Effects (HTE)

Treatment effects vary across subgroups of a factor

- Factor an effect modifier or
- Factor associated/correlated with one or more effect modifiers

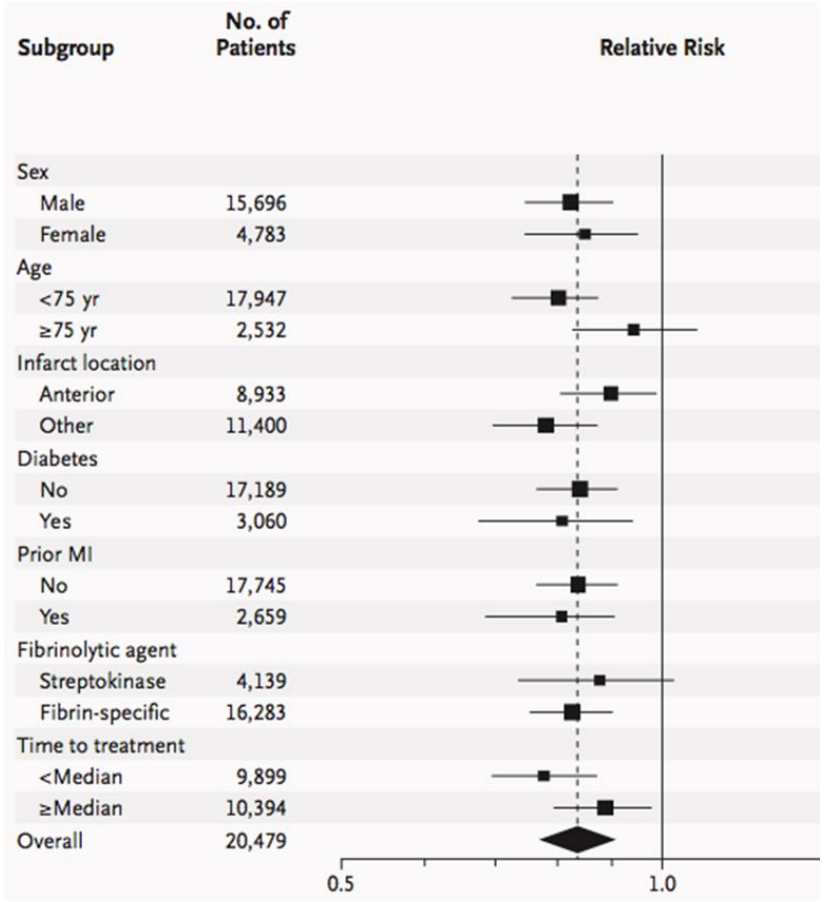
Some issues with subgroup analyses

- Clinical trials designed primarily to evaluate average treatment effect in population
- Clinical trials typically include a set of subgroup analyses defined by baseline characteristics
  - Some cases prespecified hypotheses with respect to HTE across specific subgroups
  - focus is on exploratory subgroup analyses where there is no prespecified hypothesis

Limitations with traditional approaches

- Statistical testing within subgroups
  - Low statistical power, so failure to reject null hypothesis does not indicate lack of effect
  - Does not address HTE
- Testing for interaction
  - Multiple testing → large potential for false positives
  - Low power → large potential for false negatives
- Absence of evidence of HTE considered to be evidence of consistency → no incentive to enroll a diverse population

Conventional subgroup analysis (1 of 3)



Conventional subgroup analysis (2 of 3)

- Subject to random highs and random lows
  - Estimated treatment effects vary more than underlying treatment effects
- Analysis are typically univariate or marginal - one subgrouping variable at a time
- Possibly confounded by correlation between subgrouping variables
  - If sex and age are correlated, the difference in treatment efficacy between men and women may be confounded by age
    - Groenwold (2009) - Aspirin's effect on stroke was larger in women, but women were older

Conventional subgroup analysis (3 of 3)

- Assume treatment effect equal across subgroups (unless compelling evidence that they differ). When estimating treatment effect in interested subgroup
  - Equal relevancy of outcomes for patient outside interested subgroup outcome and patient in interested subgroup
  - Under this assumption analysis (estimation of treatment effect) is simple, easy
- OR use only data from patients in interested subgroup to estimate the treatment effect for interested subgroup
  - Patient outside interested subgroup outcome provides no information (no relevancy)
  - Under this assumption analysis (estimation of treatment effect) is simple, easy

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 trial 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?
- Is there consistency of treatment effect?
- 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?

Drug Trials Snapshots

Purpose of Drug Snapshots

- Satisfy a congressional mandate
- Provide information to public on who participated in clinical trials for new molecular entities and original biologics
- Also includes information on study design, efficacy and safety results, subgroup analysis and whether there were differences among sex, race, and age subgroups and any other appropriate subgroup

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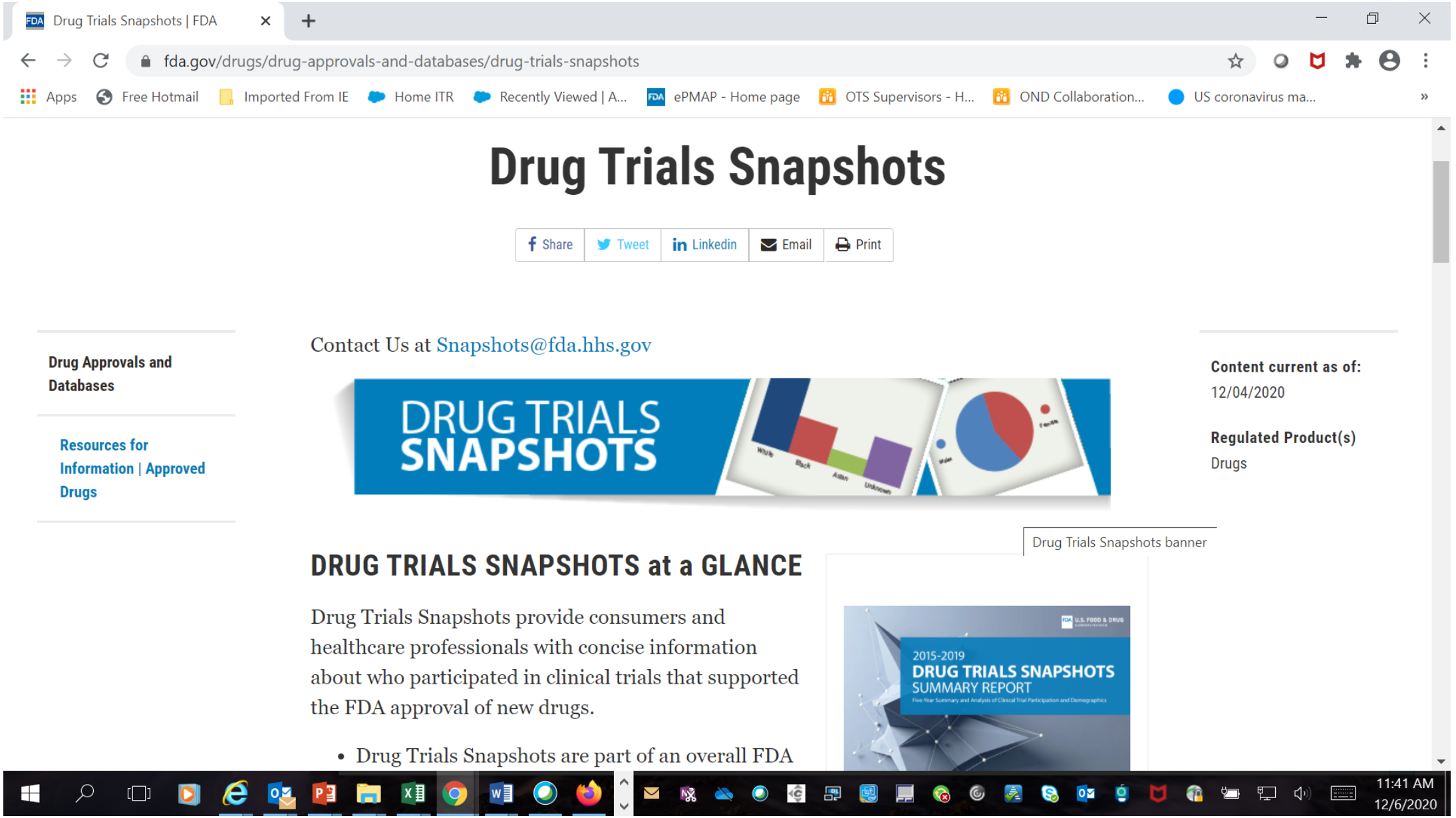
Audience

- Public, External stakeholders
- Should consider audience when constructing a DTS
  - Interest in treatment effect they may expect or in treatment effect someone like them may expect



https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

Impact Story and relevancy of results outside an interested subgroup

Drug Trials Snapshots

- 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

Treatment Decisions

- Physicians make treatment decisions on past experience with patients

New Drug

- Sex may or may not be an effect modifier
- No other factor is considered as a possible effect modifier
- Physician has experience on the use of the new drug and outcomes in 2 males and 2 females
- The next patient, a female, is prescribed the new drug from that physician. What can she expect?
  - Probably use information from all four previous patients.
  - Outcomes from females may be more relevant than the outcomes from males.

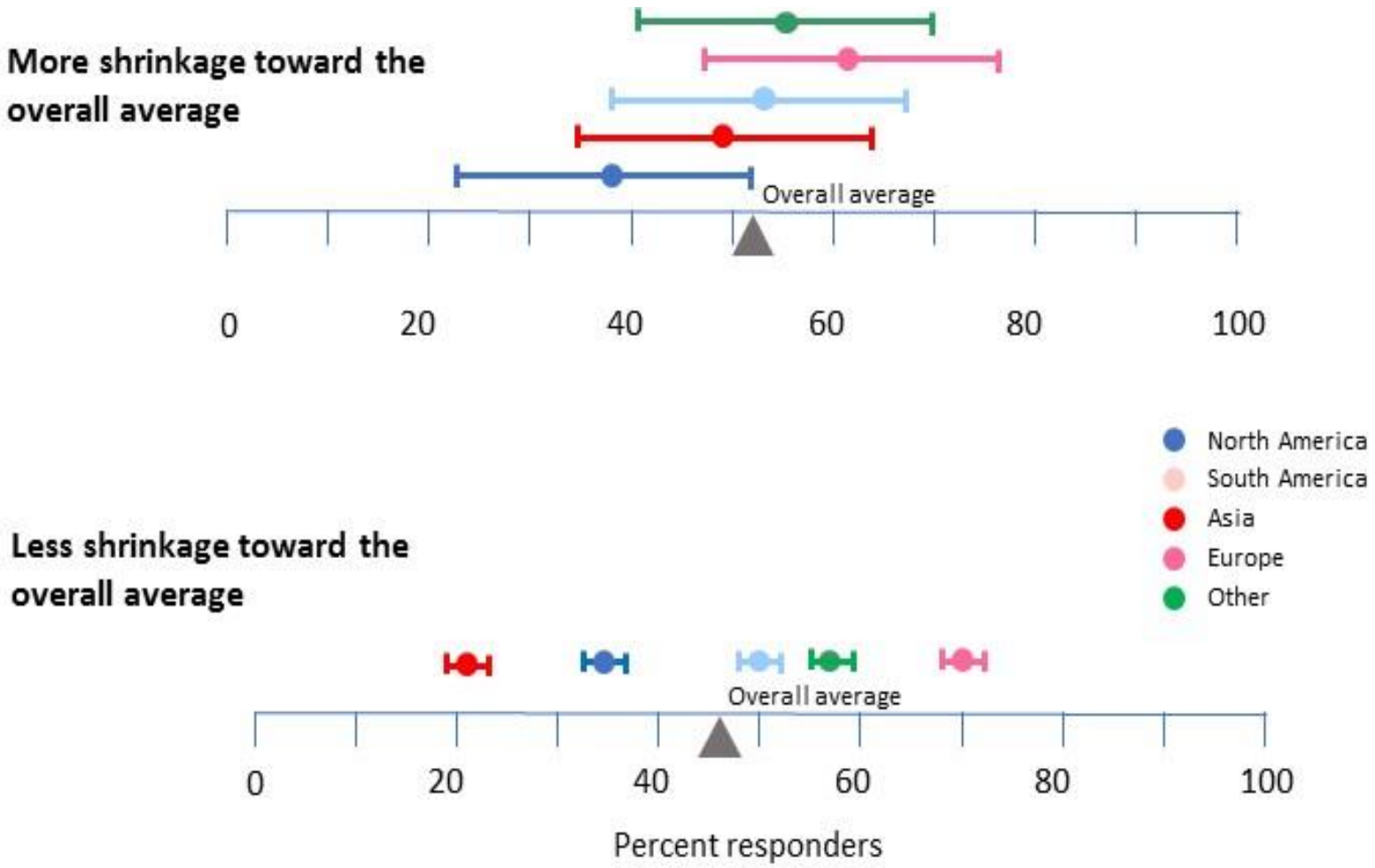
As Previous Experience Grows

- Observe the outcomes from more and more males and females
- The relevancy of the results from males in what the next female can expect. Depends on
  - How similar the results from males are to the results from females
  - How much data on females

Shrinkage Estimation using Bayesian Hierarchical Models

- Shrinkage estimation through Bayesian Hierarchical Models works this way
- Relevancy of outcomes outside an interested subgroup (and how much is “borrowed/leveraged”) depends on
  - similarity of results outside interested subgroup to results within interested subgroup
  - how much data collected within interested subgroup
  - Raw sample estimated treatment effects are “shrunk” towards the overall estimated treatment effect

How much shrinkage/borrowing



Properties of Shrinkage Estimation

- Greater precision
  - narrower 95% CIs
- Quantitatively addresses random highs and random lows
  - Sample estimated treatment subject to random highs and random lows

Lipsky AM, Gausche-Hill M, Vienna M, Lewis RJ. The importance of "shrinkage" in subgroup analyses. Ann Emerg Med. 2010;55:544–52. https://www.sciencedirect.com/science/article/pii/S0196064410000053

Example

Example 1: LEADER trial

- Cardiovascular outcome trial
- Liraglutide vs. placebo
- Time to first major adverse cardiac event
- Rule out a hazard ratio greater than 1.3

- Overall Result: HR =0.87 95% CI (0.78, 0.97)

Subgroup analyses by region – in isolation

Region	Results
	HR (95% CI)
Asia	0.62 (0.37, 1.04)
Europe	0.82 (0.68, 0.98)
North America	1.01 (0.83, 1.22)
The Rest of The World	0.83 (0.68, 1.03)

Shrinkage Analysis

	Sample estimate			Bayes Shrinkage estimate	
Region	HR	95% CI		HR	95% CI
Asia	0.62	(0.37, 1.04)		0.80	(0.59, 1.09)
Europe	0.82	(0.68, 0.98)		0.84	(0.71, 0.98)
North America	1.01	(0.83, 1.22)		0.94	(0.79, 1.12)
The Rest of the World	0.83	(0.68, 1.03)		0.85	(0.72, 1.00)

Shrinkage Analysis

	Sample estimate			Bayes Shrinkage estimate	
Region	HR	95% CI		HR	95% CI
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Europe	0.82	(0.68, 0.98)		0.84	(0.71, 0.98)
North America	1.01	(0.83, 1.22)		0.94	(0.79, 1.12)
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Concluding Comments

Concluding Remarks

- New current questions, issues and approaches to heterogenous treatment effects
- Make use of better software and graphics