Targeting interventions: transporting subgroup analyses of RCTs to inform implementation

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Introduction

Subgroup analyses of RCTs inform implementation of new interventions

- Efficient resource prioritization
- Avoid causing harm
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However, trial populations rarely resemble the target population of interest!
Pre-Exposure Prophylaxis (PrEP)

- Daily oral Truvada (FTC/TDF)
- > 90% efficacy under high adherence

The WHO has recommended the use of PrEP for all at-risk individuals.
iPrEx

2499 participants:
   2174 men
   325 transgender women

ITT analysis: 44% reduction in HIV incidence among those randomized to PrEP compared to placebo.

Subgroup analysis found no benefit of randomization in transgender women, likely due to low drug concentrations.
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- Is PrEP cost-effective in trans women?
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iPrEx

San Francisco
Boston
Guayaquil
Lima
Rio de Janeiro
Sao Paulo
Chiang Mai
Cape Town
The iPrEx study population is unlikely to represent any realistic target population!
Target Populations: HIV-negative participants from Latino MSM Community Involvement Study

- 473 Latino MSM and transgender women (San Francisco; Chicago) recruited via respondent-driven sampling
- Computer assisted self-administered interviews collected information about sexual behavior, substance use, HIV testing, and demographics
- Chicago and San Francisco treated as distinct target populations
Question and Target Parameter

What would the effect heterogeneity between transgender women and MSM have been had the iPrEx trial been conducted in each of our target populations
Where $A$ is treatment assignment, $Y$ is incident HIV infection, $G$ is gender, and $W'$ is a vector of baseline covariates that comprises age, education, number of partners in the past 6 months, preferred sexual role, and alcohol use.
Notation

We use $S = 0$ to denote the target population(s) and $S = 1$ for the iPrEx study population, and we use $G = 1$ for MSM and $G = 0$ for transgender women.

We define the average causal effect of randomization to PrEP in the iPrEx study population as:

$$\Delta^1 = \mathbb{E}(Y \mid do(A = 1), S = 1) - \mathbb{E}(Y \mid do(A = 0), S = 1)$$

and effect heterogeneity across strata of gender on the additive scale as:

$$\Psi^1 = \mathbb{E}(\Delta^1 \mid G = 1) - \mathbb{E}(\Delta^1 \mid G = 0)$$
Target Parameter

The average causal effect in the target population is therefore:

$$\Delta^0 = \mathbb{E}(Y \mid do(A = 1), S = 0) - \mathbb{E}(Y \mid do(A = 0), S = 0)$$

And the target parameter is:

$$\Psi^0 = \mathbb{E}(\Delta^0 \mid G = 1) - \mathbb{E}(\Delta^0 \mid G = 0)$$
Identifiability

Population exchangeability (s-admissibility):

After accounting for gender and baseline covariates, the target and trial populations are exchangeable.

\[ P(Y \mid do(A), G, W', S = 0) = P(Y \mid do(A), G, W', S = 1) \]
Population positivity:

Every combination of covariates within strata of gender in the target population must be represented in the study population.

\[ P(S = 1, G \mid W') > 0 \quad \text{whenever} \quad P(W' \mid G, S = 0) > 0 \]
Given the prior selection diagram and the assumptions stated, the target parameter is identified by:

$$\sum_{W'} \mathbb{E}(Y \mid A, G, W', S = 1)P(W' \mid G, S = 0)$$
Estimation

Inverse odds of selection weighted Poisson regression to transport to each target population:

\[ IOSW_i = \begin{cases} 
\frac{P(S_i=0|W_i',G_i)}{P(S_i=1|W_i',G_i)} \times \frac{P(S_i=1,G_i)}{P(S_i=0,G_i)} & \text{if } S_i = 1 \\
0 & \text{if } S_i = 0 
\end{cases} \]
Effectiveness of randomization to PrEP by gender and population
Conclusions

• Had the iPrEx study been conducted in a population that shared the same distribution of covariates as the MSM and transgender women in the Latino MSM Community Involvement Study, we would not have observed meaningful effect heterogeneity by gender.

• To best use subgroup analyses of RCTs to inform implementation of interventions, the analyses should be transported to the desired target population.
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