Methods for Synthesizing Findings across Randomized Trials: Opportunities and Challenges for LGBT Preventive Intervention Research

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NIDA LGPT Preconference
Objectives

• To discuss the feasibility of synthesizing data sets across prevention intervention studies with outcomes in adolescence and young adulthood to examine drug use and abuse, HRSB related to HIV/AIDS and other important mental, emotional and behavioral (MEB) outcomes for LGBT youth,

• To determine methodologic steps necessary to accomplish synthesis of data sets and analysis of data with considerations related to small or selected samples, harmonization of measures

• To discuss and problem solve potential barriers including sharing of research data

• Concept of “Scientific Equity” to Address Health Disparities
NIDA Supplement to Compare US-EU School-Based Drug Prevention
C Hendricks Brown/Zili Sloboda

Collaborative Data Synthesis Methodology:
NIMH R01MH040859-25

Examine shared and unique mediator and moderator effects across multiple randomized trials

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Tatiana Perrino, University of Miami
David MacKinnon, Arizona State University

Hilda Pantin, University of Miami
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Juned Siddique, Northwestern University
Ahnalee Brincks, University of Miami
Gracelyn Cruden, University of Miami

Irwin Sandler, ASU
Bill Beardslee, Harvard
Guillermo Bernal, UPR
Velma Murry, Vanderbilt
David Brent, U Pitt
How do we build a knowledge base for Preventing Adverse Outcomes for LGBT Youth Based on Randomized Trials?

Findings from a Single, Generic Randomized Trial

- Powered for Main Effect of Intervention
- Underpowered for Most Subgroup, Moderator/Mediator Analyses

National Data

- Same Sex Sexual Behavior
  - Males 15-19: 2.5%
  - Females 15-19: 11.0%

- Sexual Identity: Homosexual/bisexual
  - Males 18-19: 2.7%
  - Females 18-19: 7.7%

Local Data

- 4-10% of Familias Unidas interventions report same sex sexual behavior

Conclusion: Single Generic Randomized Trials are Completely Underpowered to Examine Impact on an LGBT Subset.

Source: 1 Chandra et al., National Health Statistics Reports 2011
Source: 2 Personal communication, Prado & Pantin
How do we build a knowledge base for Preventing Adverse Outcomes for LGBT Youth Based on Randomized Trials?

Single Site Randomized Preventive Trial for LGBT Youth
   Early self identification, stigmatizing
   Conclusion:

Science Builds on Replication: Shared vs Unique Findings
   Multicenter Randomized Trial of all Youth, including LGBT
   Strategic, Same Protocol, (NIDA CTN, PODS, TADS)
   Variation in Impact as Function of Social Context

   Replicate Trial
   Expensive, not Innovative

   Literature Review / Meta-Analysis of Existing Trials
   Inexpensive
   Limited to What’s Published

   Synthesis of Individual Level Data Analysis Across Multiple Trials
   Relatively Inexpensive
   Full multilevel, multisite analysis

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Three Alternatives for Combining Findings Across Trials

- Meta-Analysis
- Integrative Data Analysis
- Parallel Analysis

Meta-Analysis
Combining Data in a Single Analysis
Integrative Data Analysis,
Patient Level Meta-Analysis
Parallel Data Analysis
When Is Synthesis of Multiple Trials Useful for a Subgroup Analysis (LGBT)?

• Has to do better than a subgroup analysis in a single trial

Effect on Statistical Power
Positive: Added sample size

Negative: Heterogeneity across trials
Population (and Context)
Intervention
Design
Qualitative Result

A synthesis will have increased precision over that of a single trial when
- the between variance is small, or
- the number of trials relative to number of subjects is large.

Quantitative Result

- $\text{ICC} < 4 \left(\frac{\#\text{Trials} - 1}{\text{Avg Trial Sample Size}}\right)$
  - 4 Trials: Virtually Guaranteed if $N < 240$ s’s

Conclusion: Very likely to improve precision by combining data from similar trials.

But will synthesis succeed in obtaining sufficient statistical power?

Illustration from prevention trials for youth

5 Familias Unidas Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Same Sex</th>
<th>Percent</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>30</td>
<td>4.69%</td>
<td>640</td>
</tr>
<tr>
<td>CDC</td>
<td>6</td>
<td>4.08%</td>
<td>147</td>
</tr>
<tr>
<td>Hepi-1</td>
<td>8</td>
<td>3.86%</td>
<td>207</td>
</tr>
<tr>
<td>Hepi-2</td>
<td>15</td>
<td>9.87%</td>
<td>152</td>
</tr>
<tr>
<td>DJJ</td>
<td>22</td>
<td>9.87%</td>
<td>223</td>
</tr>
<tr>
<td>N</td>
<td>81</td>
<td>5.90%</td>
<td>1369</td>
</tr>
</tbody>
</table>

Power for Detecting Impact on Total N and LGBT

<table>
<thead>
<tr>
<th>Sample</th>
<th>Low (.25)</th>
<th>Med (.5)</th>
<th>High (.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N=1369)</td>
<td>0.75</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Same Sex (N=81)</td>
<td>0.15</td>
<td>0.4</td>
<td>0.7</td>
</tr>
</tbody>
</table>
But will synthesis succeed in obtaining sufficient statistical power?

Illustration from prevention trials for youth

9 Prevention Trials measuring Same Sex Sexual Behavior

Power for Detecting Impact on Total N and LGBT

<table>
<thead>
<tr>
<th>Sample</th>
<th>Low (.25)</th>
<th>Med (.5)</th>
<th>High (.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N=4498)</td>
<td>0.88</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Same Sex (N=271)</td>
<td>0.21</td>
<td>0.65</td>
<td>0.9</td>
</tr>
</tbody>
</table>

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Suggested Conclusion

• Enough data are now available to conduct a meaningful synthesis of the effects of existing prevention programs on drug and sex risk behavior among those engaged in same sex sexual behavior.
• Likely would require combining data from heterogeneous interventions
Some Examples of Integrative Data Analysis: Antidepressants (Fluoxetine) and Suicide in Youth

4 Youth Trials N = 708, Measures = 2536

• Depression Remission Rates for Youth 46% Fluoxetine, 16% Placebo

• For Youth and Adults, Suicide Symptoms Decreases over time for both Fluox & Placebo

• For Adults, Fluox decreased Suicide Sx faster than Placebo did, and mediated by Depressive Sx

• For Youth, Fluox did not decrease Suicide Sx faster than Placebo.

(Gibbons, Brown et al., 2012 a,b JAMA Psychiatry)
What are the technical challenges in synthesizing findings across randomized trials at the individual level?

1. Obtaining/Sharing the data – Tatiana Perrino
2. Handling differences in the studies
   - Population
   - Intervention
   - Design
     - Harmonizing different measures
       -- George Howe
3. Statistical Analysis
   - Mediation – Dave MacKinnon
Obtaining/Sharing the Data

Integrative Data Analysis

Parallel Data Analysis

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Parallel Data Analysis

• Use when it is not possible to obtain all datasets,
• For “Holdout” datasets, the trialists are still willing to conduct their own analyses on their data
• Specify exactly how the statistical analysis needs to be done on “Holdout” datasets
• Obtain summary results from these “Holdout” datasets
• Synthesize these summaries together in a combined analysis, accounting for heterogeneity
How can we best handle differences in populations, interventions, and trial designs, as well as limitations of dealing with small sample sizes?

**Trial Designs: The Simple Problem**

Trials have different observation times since start of trial

- **Trial 1:** 3 months, 6 months, 12 months
- **Trial 2:** 3 months, 9 months, 18 months
Comparable Analyses using Linear Growth Models

Trial 1: 0, 3 months, 6 months, 12 months
Trial 2: 0, 3 months, 9 months, 18 months

\[ Y_{ijt} = a_{ij} + b_{ij} t + \varepsilon_{ijt} \]

\[ b_{ij} = u_j + v_j \text{ Treatment}_{ij} + \delta_{ij} \]

\[ v_j = \beta + \xi_j \]

Brown et al., 2013 Prev Sci

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Differences in Interventions and Populations (including Context)

• Remove Unusual or Outlying Studies
• Use trial level measures as covariates, moderators: school climate
• Model heterogeneity
“Scientific Equity”

--- Equality in the amount of scientific knowledge that is produced to understand both the causes and solutions to health inequities (Brown et al. In Press, 2013).

-- Application of knowledge to narrowing the health and health service gap between culturally and linguistically diverse disparity populations in the US.

While there is a substantial amount data to indicate that health inequities exist and that they must be addressed, we need additional research data to guide an effective strategy to achieve health equity.

Summary

• Learning what works for LGBT Populations Requires Scientific Equity
  – Strategic plan for collecting or obtaining sufficient scientific information that can inform policy and practice

• Synthesis of findings from multiple trials based on individual level data
  – Is feasible both technically and logistically
  – Is cost effective and potentially powerful enough to answer key intervention questions for LGBTQ
    • Requires a strategy to determine which studies should be included and what data management and analyses need to be done
    • Supplement longitudinal followups to collect data
    • Support data sharing, data management, and analysis

• Key issues involve determining what mediating and moderating factors affect outcomes?
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Julie Totten- Families for Depression Awareness
Yanira Garcia-Barcena- Librarian

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