Methods: Mind the Gap
Webinar Series

Challenges Associated With Multiple Outcome Definitions in Clinical Research

Presented by
Evan Mayo-Wilson, D.Phil.
Johns Hopkins Bloomberg School of Public Health
Sources of support

European Social Research Council (ESRC)

*Laura and John Arnold Foundation

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National Institutes of Health and Care Excellence (NICE, UK)

Swedish Board of Health and Welfare (Socialstyrelsen)

*Patient Centered Outcomes Research Institute (PCORI)

*Robert Wood Johnson Foundation

*U.S. Food and Drug Administration (FDA)

*Current
## Multiple Data Sources (MUDS) Investigators

### Steering Committee
- Dickensin, Kay (KD)
- Fusco, Nicole (NF)
- Li, Tianjing (TL)
- Mayo-Wilson, Evan (EMW)
- Tolbert, Elizabeth (ET)

### Protocol development, study implementation
- Cowley, Terrie (TC)
- Haythornthwaite, Jennifer (JH)
- Hong, Hwanhee
- Payne, Jennifer (JP)
- Singh, Sonal (SS)
- Stuart, Elizabeth (ES)
- EMW, KD, TL, NF, ET, JE

### Data acquisition
- Bertizzolo, Lorenzo (LB)
- Ehmsen, Jeffery (JE)
- Gresham, Gillian (GG)
- Heyward, James (JHe)
- Lock, Diana (DL)
- Rosman, Lori (LR)
- Suarez-Cuervo, Catalina (CS)
- Twose, Claire (CT)
- KD, NF, EMW, TL, SV

### Systematic Review Data Repository
- Jap, Jens (JJ)
- Lau, Joseph (JL)
- Smith, Bryant (BS)

### Ancillary studies
- Golozar, Asieh (AG)
- Hutfless, Susie (SH)
- EMW, KD, TC

### Analysis and interpretation of data
- Canner, Joseph (JC)
- Guo, Nan (NG)
- Hong Hwanhee (HH)
- Stuart, Elizabeth (ES)
- NF, EMW, KD, TL
Overview

- Concerns about multiple outcomes & analyses (multiplicity)
- Evidence of multiplicity in clinical trials
- Strategies to address multiplicity
A replication crisis?

https://www.buzzfeednews.com/article/stephaniemlee/brian-wansink-cornell-p-hacking
Replication project

Open Science Collaboration, 2015. DOI: 10.1126/science.aac4716
“Multiplicity, combined with incomplete reporting, might be the single largest contributor to the phenomenon of nonreproducibility, or falsity, of published claims.”

Open Science Collaboration, 2015. DOI: 10.1126/science.aac4716

Goodman, et al., 2016. DOI: 10.1126/scitranslmed.aaf5027
PUBLICATION DECISIONS AND THEIR POSSIBLE EFFECTS ON INFERENCES DRAWN FROM TESTS OF SIGNIFICANCE
—OR VICE VERSA*

THEODORE D. STERLING
University of Cincinnati

There is some evidence that in fields where statistical tests of significance are commonly used, research which yields nonsignificant results is not published. Such research being unknown to other investigators may be repeated independently until eventually by chance a significant result occurs—an “error of the first kind”—and is published. Significant results published in these fields are seldom verified by independent replication. The possibility thus arises that the literature of such a field consists in substantial part of false conclusions resulting from errors of the first kind in statistical tests of significance.
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### TABLE 31

| Journals: All Issues From January To December | Total Number of Research Reports (1) | Number of Research Reports Using Tests of Significance (2) | Number of Research Reports that Reject $H_0$ with $Pr(E|H_0) \leq 0.05$ (3) | Number of Research Reports that Fail to Reject $H_0$ (4) | Number of Research Reports That are Replication of Previously Published Experiments (5) |
|---------------------------------------------|-----------------|---------------------------------|-------------------------------|------------------|----------------------------------|
| Experimental Psychology (1955)              | 124             | 106                             | 105                           | 1                | 0                                |
| Comparative and Physiological Psychology (1956) | 116             | 94                              | 91                            | 3                | 0                                |
| Clinical Psychology (1955)                  | 81              | 62                              | 59                            | 3                | 0                                |
| Social Psychology (1955)                    | 39              | 32                              | 31                            | 1                | 0                                |
| **Total**                                   | **362**         | **294**                         | **286**                       | **8**            | **0**                            |
Concerns about multiplicity and reporting bias in clinical trials

Chalmers, 1977. DOI: 10.1056/NEJM197701132960214
Concerns about multiplicity and reporting bias in clinical trials

**Randomize the First Patient!**

To the Editor: The issue of September 2 of the New England Journal of Medicine contains three articles and two editorials that beautifully illustrate the importance of randomizing the first patient when new therapies are introduced for human beings. The therapeutic trial of human leukocyte interferon in four patients with chronic active patients could have been treated in the more ethical and scientific manner of a controlled trial by now. Also, there ought to be at the very least some better method of centrally recording the sporadic individual trials now going on.

Thomas C. Chalmers, M.D.
Mount Sinai Medical Center
New York, NY 10029

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The “File Drawer Problem” and Tolerance for Null Results

Robert Rosenthal
Harvard University

For any given research area, one cannot tell how many studies have been conducted but never reported. The extreme view of the “file drawer problem” is that journals are filled with the 5% of the studies that show Type I errors, while the file drawers are filled with the 95% of the studies that show non-significant results. Quantitative procedures for computing the tolerance for filed and future null results are reported and illustrated, and the implications are discussed.
Concerns about multiplicity and reporting bias in clinical trials

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Editorial
Toward Prospective Registration of Clinical Trials

Curtis L. Meinert, PhD
Concerns about multiplicity and reporting bias in clinical trials

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Summary of Costs of HARKing

Several potential costs of HARKing have been identified, including:
1. Translating Type I errors into hard-to-eradicate theory.
2. Propounding theories that cannot (pending replication) pass Popper’s disconfirmability test.
3. Disguising post hoc explanations as a priori explanations (when the former tend also be more ad hoc, and consequently, less useful).
4. Not communicating valuable information about what did not work.
5. Taking unjustified statistical licence.
6. Presenting an inaccurate model of science to students.

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Kerr, 1998. DOI: 10.1207/s15327957pspr0203_4

New York, NY 10029

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Mount Sinai Medical Center
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Mills, 1993. DOI: 10.1056/NEJM199310143291613
Kerr, 1998. DOI: 10.1207/s15327957pspr0203_4
Chan, 2004. DOI: 10.1001/jama.291.20.2457
Emphasis on “significance” over time

Figure 1. Proportion of MEDLINE Abstracts Reporting at Least 1 P Value in the Period 1990-2015

Chavalarias, 2016. DOI: 10.1001/jama.2016.1952
Multiple data sources

Public data sources
- Short report (e.g., letter, conference abstract)
- Journal article
- Trial registration
- Results on trial registry
- Information from regulators

Non-public data sources
- Unpublished manuscript
- Individual participant data (IPD)
- Grant proposal
- Study protocol
- Case report form
- Memos and emails

Mayo-Wilson, 2015. DOI: 10.1186/s13643-015-0134-z OA

Doshi, 2013. DOI: 10.1136/bmj.f2865
Gabapentin: results for “primary” outcomes differ between sources

Primary outcome in unpublished research report (red)

Primary outcome in published journal article (blue)

Vedula, 2009. DOI: 10.1056/NEJMsa0906126
Gabapentin: results for “primary” outcomes differ between sources

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Gabapentin: results for “primary” outcomes differ between sources

Vedula, 2009. DOI: 10.1056/NEJMsa0906126
Outcomes are defined in many ways

**Elements of an outcome on ClinicalTrials.gov**

- **Level 1 Domain**
  - Anxiety
  - Depression
  - Schizophrenia

- **Level 2 Specific Measurement**
  - Beck Anxiety Inventory
  - Hamilton Anxiety Rating Scale
  - Fear Questionnaire

- **Level 3 Specific Metric**
  - End value
  - Change from baseline
  - Time to event

- **Level 4 Method of Aggregation**
  - Continuous
    - Mean
    - Median
  - Categorical
    - Proportion of participants with decrease ≥50%
    - Proportion of participants with decrease ≥8 points

Zarin, 2011. DOI: 10.1056/NEJMsa1012065
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- Mean
- Median
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**4 outcome domains**
- Pain

**2 specific measures**
- McGill Pain Questionnaire
- Value at timepoint
- Change from baseline

**2 specific metrics**
- Continuous
- Categorical

**2 methods of aggregation**
- 32 outcomes

**2 timepoints**
- 64 outcomes

Zarin, 2011. DOI: 10.1056/NEJMsa1012065
Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
## Multiple analyses lead to *multiple results for the same outcome*

<table>
<thead>
<tr>
<th>Analysis population</th>
<th>Handling missing data</th>
<th>Methods of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants eligible to be included in the analysis (e.g., people who took one dose, everyone randomized)</td>
<td>Methods to account for missing data, including missing items and missing cases (e.g., multiple imputation, last observation carried forward)</td>
<td>Statistical methods, including analysis model, procedures (e.g., transformations, adjustments), and covariates included in the analysis</td>
</tr>
</tbody>
</table>

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
Multiple Data Sources (MUDS) Study Design

- Two case studies:
  - Gabapentin for neuropathic pain
  - Quetiapine for bipolar depression

- Participants & investigators masked

- Placebo-controlled, parallel RCTs

- Comprehensive searches for published and unpublished data

Mayo-Wilson, 2015. DOI: 10.1186/s13643-015-0134-z OA
## Characteristics of eligible trials

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of trials</strong></td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td><strong>Dates of reports</strong></td>
<td>1997 to 2013</td>
<td>2003 to 2014</td>
</tr>
<tr>
<td><strong>No. public reports / No. all reports</strong></td>
<td>68/74</td>
<td>46/50</td>
</tr>
<tr>
<td><strong>Individual participant data (No. trials, % of total)</strong></td>
<td>6 (29%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td><strong>Trial characteristics (No. trials, % of total)</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer-funded</td>
<td>14 (67%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>≥3 groups</td>
<td>11 (52%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Multi-center</td>
<td>14 (67%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>English language</td>
<td>20 (95%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td><strong>Number of participants randomized (median, range)</strong></td>
<td>150 (26 to 452)</td>
<td>526 (100 to 802)</td>
</tr>
<tr>
<td><strong>Sources of data for each trial (No. trials, % of all trials)</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only public</td>
<td>15 (71%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Only non-public</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Both public &amp; non-public</td>
<td>5 (24%)</td>
<td>4 (57%)</td>
</tr>
</tbody>
</table>

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.07.014
How many outcomes are there in clinical trials?

21 gabapentin trials

6 with non-public sources

4 Outcome domains

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How many outcomes are there in clinical trials?

Multiple measures

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How many outcomes are there in clinical trials?

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How many outcomes are there in clinical trials?

Multiple metrics

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How many outcomes are there in clinical trials?

Multiple methods of aggregation

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How many outcomes are there in clinical trials?

214 outcomes

1230 results

305 (25%) publicly reported

More hidden...

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
Multiple outcomes and analyses in trials of gabapentin for neuropathic pain

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
Consequences of multiplicity for systematic reviews

Item 1: Histogram showing the distribution of means (SMDs) from meta-analyses using one continuous effect estimate per study (selected at random)

Item 2: Average of the mean effects (SMDs)

Item 3: 95% confidence interval (CI) corresponding to the mean effects (SMDs) in the histogram, including lower (<) and upper (>) limits.

Item 4: The smallest and largest possible treatment effect from a meta-analysis (with associated 95% CI) calculated by selecting the most extreme results from any report about each included trial.
Consequences of multiplicity for systematic reviews

34 trillion possible meta-analyses of “pain” domain i.e., combinations of the same trials

Key

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Consequences of multiplicity for systematic reviews

- Wide distribution of possible effects

- Largest possible: Big effect, “significant”

- Smallest possible: Small effect, “not significant”

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.07.014
Core outcome sets for clinical trials and systematic reviews

http://www.comet-initiative.org/about/overview
Boers, 2014. DOI: 10.1016/j.jclinepi.2013.11.013

“minimum set of outcome measures that must be reported in all RCTs in a given health condition”
Core outcome sets: IMMPACT recommended outcomes

IMMPACT (pain trials)

1) Pain
   a. 11-point (0-10) rating of pain intensity
   b. Usage of rescue analgesics
   c. Categorical rating of pain intensity

2) Physical functioning (either one of two measures)
   a. Multidimensional pain inventory interference scale
   b. Brief Pain Inventory interference items

3) Emotional functioning (at least one one of two measures)
   a. Beck Depression Inventory
   b. Profile of Mood States

4) Participant ratings of global improvement and satisfaction with treatment
   a. Patient Global Impression of Change

5) Symptoms and adverse events
   a. Passive capture of spontaneously reported adverse events

6) Participant disposition

Supporting Investigators in registering and reporting results

Faced with public pressure, research institutions step up reporting of clinical trial results

By CHARLES PILLER @piller and TALIA BRONShtein / JANUARY 9, 2018

- Account characteristics
- Policies
- Procedures
- Computer systems
- Staff

Clinical trial registration and reporting: a survey of academic organizations in the United States

Evan Mayo-Wilson, James Heyward, Anthony Keyes, Jesse Reynolds, Sarah White, Nichi Ati, G. Caleb Alexander, Audrey Omar, Daniel E. Ford and on behalf of the National Clinical Trials Registration and Results Reporting Taskforce Survey Subcommittee

Supporting Investigators in registering and reporting results

Participants

► Invited 783 “University/Organization” accounts
► 366 (47%) partially or fully completed
► Large organizations most likely to participate

Results

► 43% had a trial registration policy
► 35% had a results reporting policy
► 19% used computer software to manage records
► Median staffing 8% of one full-time equivalent

Conclusions

► Multiple outcomes, and multiple analyses, lead to many results

► Many results for an “outcome domain” create opportunities for cherry-picking

► To increase consistency, and to reduce research waste, trials and systematic reviews should use core outcome sets

► To prevent bias, outcomes and analysis plans should be registered completely and prospectively

► Institutions can support investigators in meeting registration and reporting requirements

Mayo-Wilson, 2018. DOI: 10.1002/jrsm.1277
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