Benefits and challenges of using multiple data sources in systematic reviews

Evan Mayo-Wilson, MPA, Dphil
Tianjing Li, MD, PhD
Center for Clinical Trials and Evidence Synthesis
Department of Epidemiology
Multiple Data Sources (MUDS) Investigators

**Steering Committee**
Dickersin, 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

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

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

**Ancillary studies**
Golozar, Asieh (AG)
Hutfless, Susie (SH)
EMW, KD, TC
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- Unpublished manuscript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
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► Comprehensive searches for published and unpublished data
## 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
## Characteristics of eligible trials

<table>
<thead>
<tr>
<th>Trials with each report type (No. trials, % of all trials)</th>
<th>Gabapentin</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal article about 1 trial</td>
<td>17 (81%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Journal article about ≥2 trials</td>
<td>7 (33%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Short report: conference abstract</td>
<td>10 (48%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Short report: other</td>
<td>9 (43%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Trial registration</td>
<td>5 (24%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>FDA report</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CSR-Synopsis</td>
<td>0 (0%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>CSR</td>
<td>6 (29%)</td>
<td>2 (29%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reports of manufacturer funded trials</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer-funded trials (public reports per trial, SD)</td>
<td>7.4 (6.0)</td>
<td>10.3 (8.6)</td>
</tr>
<tr>
<td>Other trials (public reports per trial, SD)</td>
<td>1.4 (0.5)</td>
<td>Not applicable</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
21 trials of gabapentin for neuropathic pain (14 with multiple reports)

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
Poor reporting of research methods

1: Individual trial report ROB items (1 to 17 reports per study)
2: Overall ROB worst case (high, unclear, low)
3: Overall ROB best case (low, unclear, high)

“Best” and “Worst” cases
Individual reports

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
Poor reporting of research methods

3: Overall ROB best case (low, unclear, high)
2: Overall ROB worst case (high, unclear, low)
1: Individual trial report ROB items (1 to 17 reports per study)

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
Results for “primary” outcomes differ between sources

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

Zarin, 2011. DOI: 10.1056/NEJMsa1012065
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

- **4 outcome domains**
  - Pain
  - 0-10 scale

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

- **2 specific metrics**
  - 16 outcomes
    - Continuous
    - Categorical

- **2 methods of aggregation**
  - 32 outcomes

- **2 timepoints**
  - 64 outcomes
    - 1 week
    - 8 weeks

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
How much multiplicity is there in clinical trials?

21 trials

6 with non-public sources

4 Outcome domains

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How much multiplicity is there in clinical trials?

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How much multiplicity is there in clinical trials?

Multiple totals and subscales

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How much multiplicity is there in clinical trials?

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How much multiplicity is there in clinical trials?

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How much multiplicity is there in clinical trials?

Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007
How much multiplicity is 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

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

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Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.07.014
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
### Guidance for systematic reviews using multiple sources

#### Challenges
- Multiple sources increase effort required for systematic reviews
- Non-public sources are time-consuming to identify and obtain
- Investigators may refuse requests to share non-public sources
- It is frequently unclear if multiple reports refer to the same study
- Double-counting trials can lead to incorrect conclusions
- A single source rarely provides complete information about trial design and trial quality ("risk of bias")
- Multiple sources may contain conflicting information about the same trial
- Sources may include the same or different results
- Different sources may include multiple results for the same outcome
- Results may depend on which sources were used for each trial
- Systematic reviews may not be reproducible unless the data and sources used are available to other researchers

#### Recommendations
- Allocate time to obtain non-public sources and to reconcile information from multiple sources
- Search for non-public sources early in the review process
- Plan for the possibility that requests to trial investigators are refused
- Ask authors to confirm which sources are related to each trial
- Check as many trial characteristics as possible to determine which sources are related to the same trials
- Include a modified PRISMA flowchart to document the selection of data sources
- Use journal articles, trial registries, regulatory reviews, and CSRs to extract information about trial design and quality
- Record the source of information about trial design and quality
- Ask investigators to clarify differences among sources
- Prioritize which source will be used if sources are contradictory (a priori)
- Use journal articles, trial registries, regulatory reviews, CSRs, and IPD to extract results
- Consider excluding results reported only in conference abstracts
- Record the source of each result
- Follow pre-specified methods for choosing among multiple outcome definitions and methods of analysis
- Describe public and non-public sources included, excluded, and awaiting assessment for each trial
- Consider the trustworthiness of the included sources when making recommendations for research and practice
- Share data sources alongside the review (e.g., as online supplements) so that other researchers can check the data and use previously non-public sources in future research

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Mayo-Wilson, et al., 2017. DOI: 10.1002/jrsm.1277
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”
Conclusions

- When multiple sources are available, the results of meta-analysis and systematic review may be sensitive to choice of source.
- Conference abstracts were useful only for identifying trials not reported elsewhere.
- Journal articles were broadly consistent with CSRs, but each source sometimes contained information not found in the other source.
- CSRs were most informative about methods.
- CSRs and IPD contained the most results information.
- IPD alone did not include enough information to understand and interpret the data.
- Obtaining and analyzing non-public sources is time consuming and requires expertise.