Transparency at the FDA
What can be learned from the data we have?

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Pew Charitable Trusts
Washington, D.C.
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Kay Dickersin’s declaration of interests

- **Grants and contracts from agencies** (completed 2017)
  - PCORI-Engagement of consumers
  - PCORI-Influence of multiple sources of data on meta-analysis
  - FDA-Centers for Excellence in Regulatory Science Innovation (GC Alexander, PI)

- **Grants and contracts from agencies** (ongoing)
  - NIH-Cochrane Eyes and Vision
  - PCORI-Consumer Summit with G-I-N North America
  - AHRQ-Consumers United for Evidence-based Healthcare
  - PCORI - Individual Participant Data Meta-analysis of progesterone for prevention of preterm birth (subcontract)
  - PCORI - Peer Review of PCORI Funded Research (subcontract)

- **Other**
  - Thomas Greene fund for research scholarship (no salary support)
From research evidence to best practices

Evidence generation → Systematic reviews → Practice policy (e.g., guidelines)

Clinical trials, observational studies → Cochrane Collaboration, EPCs, others → Professional Societies, others

Application of policy: Evidence Constraints Public’s values

Knowledge translation: Data, information, knowledge
THE RIGHT TO SEARCH FOR TRUTH IMPLIES ALSO A DUTY; ONE MUST NOT CONCEAL ANY PART OF WHAT ONE HAS RECOGNIZED TO BE TRUE.

ALBERT EINSTEIN 1879 - 1955
Research: increasing value, reducing waste 1
How to increase value and reduce waste when research priorities are set

Iain Chalmers, Michael B Bracken, Ben Djulbegovic, Silvio Garattini, Jonathan Grant, A Metin Gölmizoglu, David W Howells, John P A Ioannidis, Sandy Oliver

Research: increasing value, reducing waste 2
Increasing value and reducing waste in research design, conduct, and analysis

John P A Ioannidis, Sander Greenland, Mark A Hlatky, Muin J Khoury, Malcolm R Macleod, David Moher, Kenneth F Schulz, Robert Tibshirani

Research: increasing value, reducing waste 3
Increasing value and reducing waste in biomedical research regulation and management


Research: increasing value, reducing waste 4
Increasing value and reducing waste: addressing inaccessible research

An-Wen Chan, Fujian Song, Andrew Vickers, Tom Jefferson, Kay Dickersin, Peter C Gøtzsche, Harlan M Krumholz, Davina Gherzi, H Bart van der Worp
Institute of Medicine has recommended data sharing
We know from numerous studies that public reporting of clinical trials is less than optimal.

• Ask a clear question [population, intervention/exposure, comparator, outcome (PICO or PECO)]
• Minimize risk of bias in the included studies
• Minimize meta-bias in the systematic review
Comparing protocols to publications

Discrepancies between protocols and publications

- Sample size calculations (18/34 trials)
- Methods of handling protocol deviations (19/43)
- Missing data (39/49)
- Primary outcome analyses (25/42)
- Subgroup analyses (25/25)
- Adjusted analyses (23/28)

Source: Chan et al, BMJ 2008
MUDS examined public and non-public information for 2 cases

- Gabapentin for neuropathic pain
- Quetiapine for bipolar disorder
In MUDS, we found 21 trials that asked the question “is gabapentin is effective in relieving neuropathic pain?”

21 trials, 80 unique sources

Public sources (n=68)
- 26 journal articles
- 20 conference abstracts
- 5 trial registry entries
- 2 FDA reports
- 15 “other” reports

Non-public sources (n=12)
- 6 clinical study reports (CSRs)
- 6 individual patient datasets (IPD) (w/o codebooks)

MUDS: Public reports were unclear or disagree on participants, interventions, comparators, outcomes (PICO) examined

- **Participant**: Number randomized
- **Intervention/comparator**
- **Outcomes**:
  - Variation in measurement, metric, method of aggregation, time point
  - Adverse events not reported

MUDS: Study characteristics varied for trials with more than one report


<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Reports</th>
<th>Participants</th>
<th>Intervention and Comparator(s)</th>
<th>Time (longest follow-up)</th>
<th>Trial funding</th>
<th>Financial Interests</th>
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Substantive difference across reports: X
Difference in completeness across reports: O
No difference across reports: 

Not applicable (only one report)
Selective outcome reporting: P Values for protocol-defined primary outcome vs. in main publication

Standards we suggest for asking a clear question (PICO/PECO)

<table>
<thead>
<tr>
<th>Problems with PICO/PECO</th>
<th>Standard</th>
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<tbody>
<tr>
<td>Populations, interventions/exposures, outcomes (PICO/PECO) <strong>reported in multiple sources</strong>, each different</td>
<td>Make sure ≥1 reliable public source accessible through good indexing. Reports should report consistently</td>
</tr>
<tr>
<td><strong>PICO/PECO not clearly described</strong></td>
<td>Study protocol should be available. Study should be reproducible, reporting standards followed</td>
</tr>
<tr>
<td><strong>PICO/PECO not what is in protocol</strong></td>
<td>Pre-specified items should be publicly available, amendments made to protocol, and <em>post hoc</em> decisions noted</td>
</tr>
<tr>
<td>Findings cannot be averaged because <strong>public data not meta-analyzable</strong></td>
<td>Data should be completely presented and made public (e.g., individual participant data)</td>
</tr>
</tbody>
</table>

Trial reporting is less than optimal

- Ask a clear question [population, intervention/exposure, comparator, outcome (PICO or PECO)] (harder than it looks)
- Minimize risk of bias in the included studies
- Minimize meta-bias in the systematic review
Risk of bias in multiple reports

Risk of bias: Most reports “unclear”


Elise Diard conceived of and drew the risk of bias figure.
### Standards we suggest for minimizing risk of bias in the included studies

<table>
<thead>
<tr>
<th>Problems with quality of individual studies (risk of bias)</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many studies unclear on key quality items</td>
<td>Make protocols and CSRs available. Reporting standards should be followed</td>
</tr>
<tr>
<td>Analysis of “missing” data is a key area for focus</td>
<td>Make CSRs, metadata available so that statistical methods are clearly described.</td>
</tr>
</tbody>
</table>

Trial reporting is less than optimal

- Ask a clear question [population, intervention/exposure, comparator, outcome (PICO or PECO)] (harder than it looks)
- Minimize risk of bias in the included studies
- Minimize meta-bias in the systematic review
Outcome = mean difference between groups in pain intensity at 8 wks. When 95% confidence intervals for the treatment effects appear on both sides of the dashed line, it would be possible to conduct a meta-analysis with either a statistically significant or statistically nonsignificant result.
## Standards we suggest for minimizing metabias in the systematic review

<table>
<thead>
<tr>
<th>Source of metabias</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not all study methods and results are made public</td>
<td>Publish or make public methods and results from all studies</td>
</tr>
<tr>
<td>Publication bias</td>
<td>Report all studies, regardless of findings</td>
</tr>
<tr>
<td>Selective reporting bias</td>
<td>Report what was planned and any exploratory outcomes and results</td>
</tr>
<tr>
<td>Non-public data shows more benefits and harms</td>
<td>Make all data public (eg, IPD, CSRs)</td>
</tr>
</tbody>
</table>

How making IPD, CSRs, pooled data sets and final research reports publicly available will improve patient care

- **Methods**
  - Population, Intervention, Comparison intervention, Outcomes
  - Risk of bias items
  - Other items related to study reproducibility

- **Results**
  - Data on potential benefits and harms consistently and fully reported