Selecting outcomes for clinical trials -
A case study using Cochrane systematic
reviews on HIV/AIDS

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Outline

• Background
• Objectives
• Methods
• Results
• Conclusions
Importance of outcomes in clinical trials

• An **event** or **measure** in study participants that is used to assess the **effectiveness** and/or **safety** of the intervention being studied.

  Meinert CL. *Clinical Trials Dictionary. 2nd ed.*

• A *priori* selection of outcomes is critical:
  – Sample size
  – Reduction of multiple comparisons
  – Reduction of outcome reporting bias
How do clinical trialists select outcomes?

Considerations
• Clinically relevance
• Patient relevance
• Treatment effect
• Adequacy of follow up
• Resources - sample size, costs

(DeMets 1980, Sinha 2012, Williamson 2012)

Available outcomes and guidance
• Other clinical trials
• Stakeholders – e.g., clinicians, patients, trialists
• Regulatory guidance – FDA, NIH (e.g., PROMIS)
• Core Outcome Measures in Effectiveness Trials (COMET)
• Others
Systematic review

Systematic review process

Synthesized evidence
Patient relevance of outcomes

Patient-reported outcomes (PRO)
• Obtained directly from the study subject
• Without amendment/interpretation
• Self-report/interview

(Food and Drug Administration 2009)

Patient-important outcomes (PIO)
• Outcomes that patients value directly, usually in contrast to surrogate, substitute, or physiologic outcomes
  (JAMA Evidence. Patient-important outcomes)
• ..outcomes that people notice and care about...
  (PCORI. Definitions of PCOR)
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Objectives

1. To examine the utility of systematic reviews for providing information about outcomes examined across a group of clinical trials in a subject area (HIV/AIDS)

2. To examine the patient-relevance (i.e., patient-reportedness and patient-importance) of outcomes examined in systematic reviews in a subject area (HIV/AIDS)
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Methods

Systematic reviews examined
• All Cochrane reviews published by the HIV/AIDS Review Group (June 2013)

Data extracted
• Review characteristics (e.g., year, interventions)
• Outcome characteristics (Methods section) – all outcomes
  • Outcome domain (name)
  • Patient-reportedness – yes/no
  • Patient-importance – yes/no

Data extraction process
• Dual independent data extraction using Google Forms®
• Discrepancy resolution by consensus
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Systematic reviews examined

**Systematic review characteristics**
- N=140 documents
  - 99 completed systematic reviews
  - 41 protocols
- Published 2008-2013

**RCTs included in systematic reviews**
- 98.6% included RCTs
- Number of trials per completed review
  - Median = 5
  - IQR = 2-10
  - Range = 0-44
# Interventions addressed

<table>
<thead>
<tr>
<th>Interventions addressed</th>
<th>Number of systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td><strong>All reviews</strong></td>
<td>140</td>
</tr>
<tr>
<td>Drugs</td>
<td>79</td>
</tr>
<tr>
<td>Behavioral interventions (including counseling)</td>
<td>27</td>
</tr>
<tr>
<td>Procedures</td>
<td>12</td>
</tr>
<tr>
<td>Policy</td>
<td>10</td>
</tr>
<tr>
<td>Healthcare services</td>
<td>8</td>
</tr>
<tr>
<td>Education</td>
<td>7</td>
</tr>
<tr>
<td>HIV testing</td>
<td>7</td>
</tr>
<tr>
<td>Other (e.g., vaccines, social marketing interventions)</td>
<td>14</td>
</tr>
</tbody>
</table>
Number of outcome domains

- Median = 7, range (1-30) outcome domains per review
- 294 unique outcome domains used 1140 times!

Yikes!!!
Main categories of outcome domains

- Clinical/biological: 160 (54%)
- Behavioral: 51 (17%)
- Mental health/sociological: 17 (6%)
- Antiretroviral prophylaxis/treatment: 10 (3%)
- Health services access/uptake: 9 (3%)
- Knowledge: 8 (3%)
- Testing/counseling: 8 (3%)
- Attitude: 5 (2%)
- Preference/Satisfaction: 5 (2%)
- Adverse: 5 (2%)
- Economic: 3 (1%)
- Quality of life: 1 (1%)
- Adherence-related: 1 (1%)
- Other: 11 (4%)

N=294 unique outcome domains
Classification of 160 clinical/biologic outcome domains

- Clinical symptoms: 10
- Clinical signs: 7
- Anthropometric measures: 28
- Laboratory measures: 19
- Clinical diagnoses: 51
- Pregnancy, postpartum, and neonatal: 15
- Survival-related: 4
- Death-related: 13
- Other clinical: 13
Patient-relevance of outcome domains

• Reviews with at least one patient-reported outcome domain
  – 45/140 reviews (32.1%)

• Reviews with at least one patient-important outcome domain
  – 136/140 reviews (97.1%)
Evidence-based healthcare

Systematic review process

Synthesized evidence
## 10 most frequent patient-reported outcome domains

<table>
<thead>
<tr>
<th>Patient-reported outcome domain</th>
<th>Number of reviews N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Quality of life</td>
<td>39 (27.9)</td>
</tr>
<tr>
<td>2 Major/serious adverse events</td>
<td>25 (17.9)</td>
</tr>
<tr>
<td>3 Adverse events (specified)</td>
<td>19 (13.6)</td>
</tr>
<tr>
<td>4 Patient intervention acceptability</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>5 Depression/depressive symptoms</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>6 Condom use (male condoms)</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>7 Condom use (female condoms)</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>8 HIV-related knowledge</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>9 Unprotected sex (type unspecified)</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>10 Number of sexual partners</td>
<td>8 (5.7)</td>
</tr>
</tbody>
</table>
### 10 most frequent patient-important outcome domains

<table>
<thead>
<tr>
<th>Patient-important outcome domain</th>
<th>Number of reviews N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Mortality/all-cause mortality</td>
<td>68 (48.6)</td>
</tr>
<tr>
<td>2  Adverse events</td>
<td>57 (40.7)</td>
</tr>
<tr>
<td>3  Quality of life</td>
<td>39 (27.9)</td>
</tr>
<tr>
<td>4  Major/serious adverse events</td>
<td>26 (18.9)</td>
</tr>
<tr>
<td>5  Costs/cost-effectiveness for patients</td>
<td>25 (17.9)</td>
</tr>
<tr>
<td>6  Resistance to antiretroviral treatment</td>
<td>20 (14.3)</td>
</tr>
<tr>
<td>7  Acquisition of sexually transmitted infections (STIs)</td>
<td>17 (12.1)</td>
</tr>
<tr>
<td>8  AIDS-defining illness/event</td>
<td>17 (12.1)</td>
</tr>
<tr>
<td>9  HIV/AIDS-related mortality</td>
<td>16 (11.4)</td>
</tr>
<tr>
<td>10 Mother to child transmission of HIV</td>
<td>15 (10.7)</td>
</tr>
</tbody>
</table>
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Conclusions

• Capitalize on systematic reviews to select outcome domains
  • Identify outcomes used by other trials
  • Ensure clinical trials are useful for systematic reviews

• Consider all main categories and subcategories of outcome domains

• Consider patient-relevance of outcomes (PROs and PIOs)
Strengths

• Systematic review perspective
  – Systematic review outcomes ≠ clinical trial outcomes

• Classification of PROs and PIOs based on standard definitions
Collaborators

- Dr. Kay Dickersin (Johns Hopkins University)
- Dr. Tianjing Li (Johns Hopkins University)
- Dr. Cesar Ugarte-Gil (Johns Hopkins University)
- Dr. George Rutherford (University of California San Francisco)
- Dr. Jimmy Volmink (Stellenbosch University)

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