

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

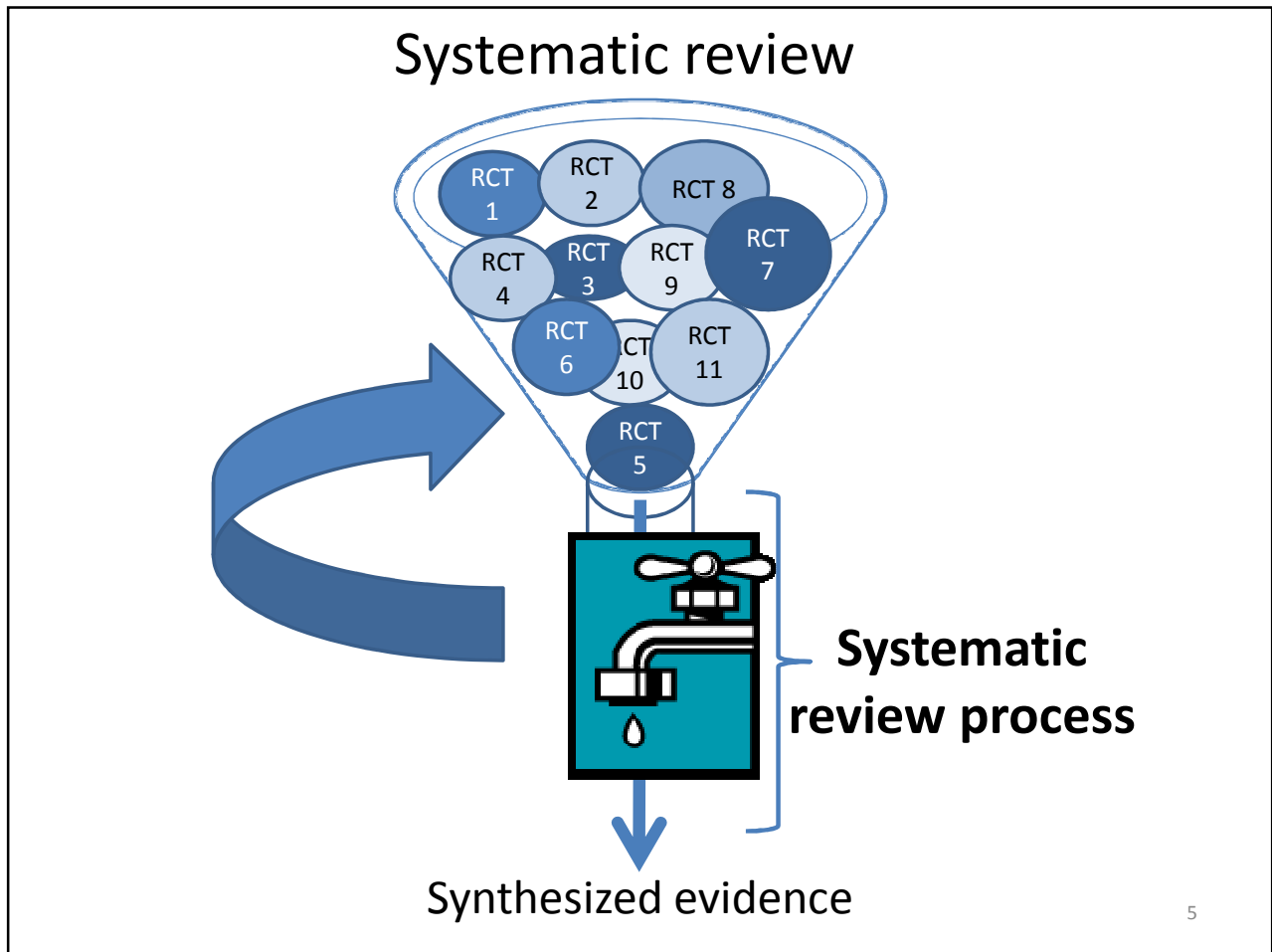
- Clinically relevance
- Patient relevance
- Treatment effect
- Adequacy of follow up
- Resources - sample size, costs



(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



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
- ..outcomes that people notice and care about...

(JAMA Evidence. Patient-important outcomes)

(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

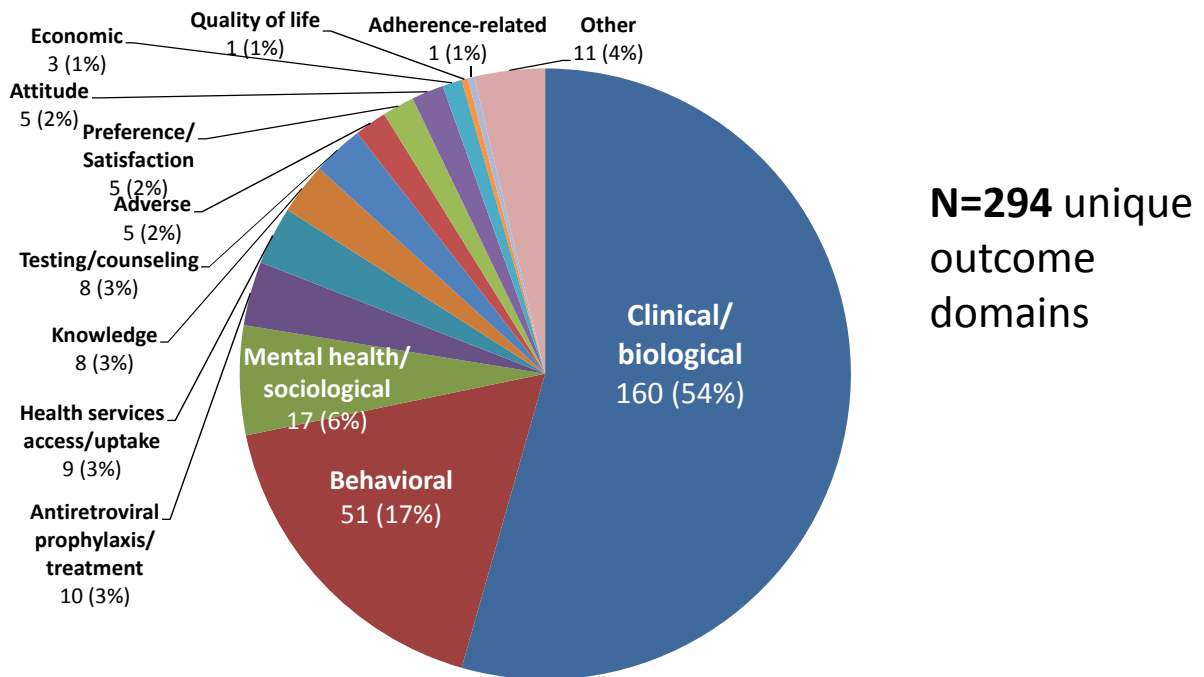
Interventions addressed	Number of systematic reviews	
	N	%
All reviews	140	(100.0)
Drugs	79	(56.4)
Behavioral interventions (including counseling)	27	(19.3)
Procedures	12	(8.6)
Policy	10	(7.1)
Healthcare services	8	(5.7)
Education	7	(5.0)
HIV testing	7	(5.0)
Other (e.g., vaccines, social marketing interventions)	14	(10.0)

Number of outcome domains

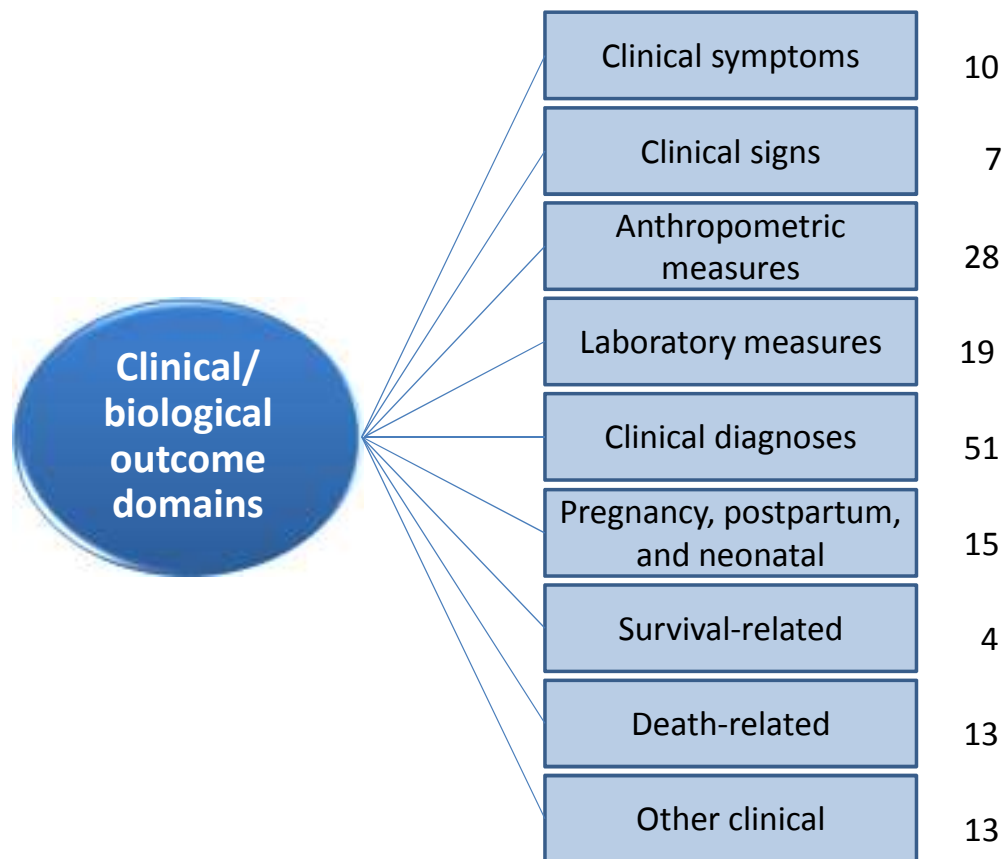
- Median = 7, range (1-30) outcome domains per review
- **294** unique outcome domains used **1140** times!

Yikes!!!

Main categories of outcome domains



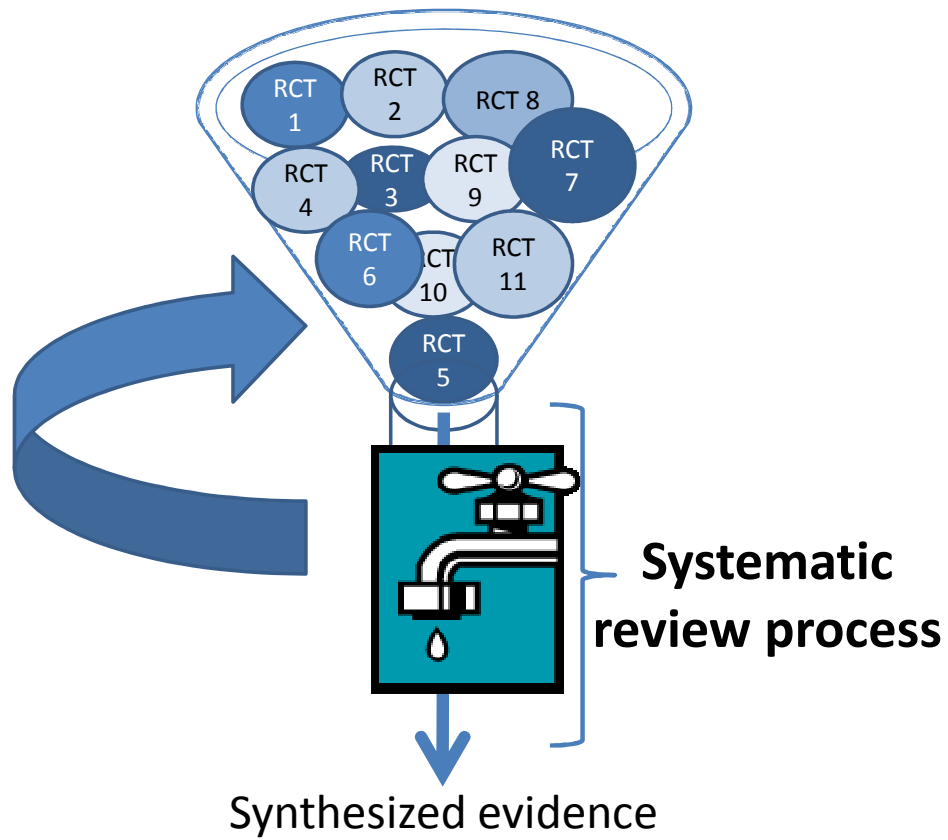
Classification of 160 clinical/biologic outcome domains



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



10 most frequent patient-reported outcome domains

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

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10 most frequent patient-important outcome domains

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

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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 \neq 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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