

Mind the Gap: Risk of Bias in Pediatric Trials

Developing an Integrated Strategy to Support
Pediatric and Perinatal Clinical Trials Across Canada

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Introduction

- Randomized controlled trials (**RCTs**) are the gold standard for decision-making regarding therapy, but they are not immune from bias.
- There is a growing body of literature documenting the limitations and methodological flaws of pediatric research.
- The introduction of bias into a trial can lead to the overestimation of treatment benefits or underestimation of treatment harms.

Objectives

- 1) To give an overview of the Cochrane Collaboration's Risk of Bias tool.
- 2) To describe a research program focused on the development and evaluation of a knowledge translation (**KT**) strategy that will increase awareness and promote methodological rigor among pediatric trialists.

Risk of Bias

- *Cochrane Risk of Bias tool*: based on empirical evidence demonstrating associations between various methodological characteristics and magnitude of effect estimates
- Six domains:
 - Sequence generation
 - Allocation concealment
 - Blinding
 - Incomplete outcome data
 - Selective outcome reporting
 - “Other” sources of bias

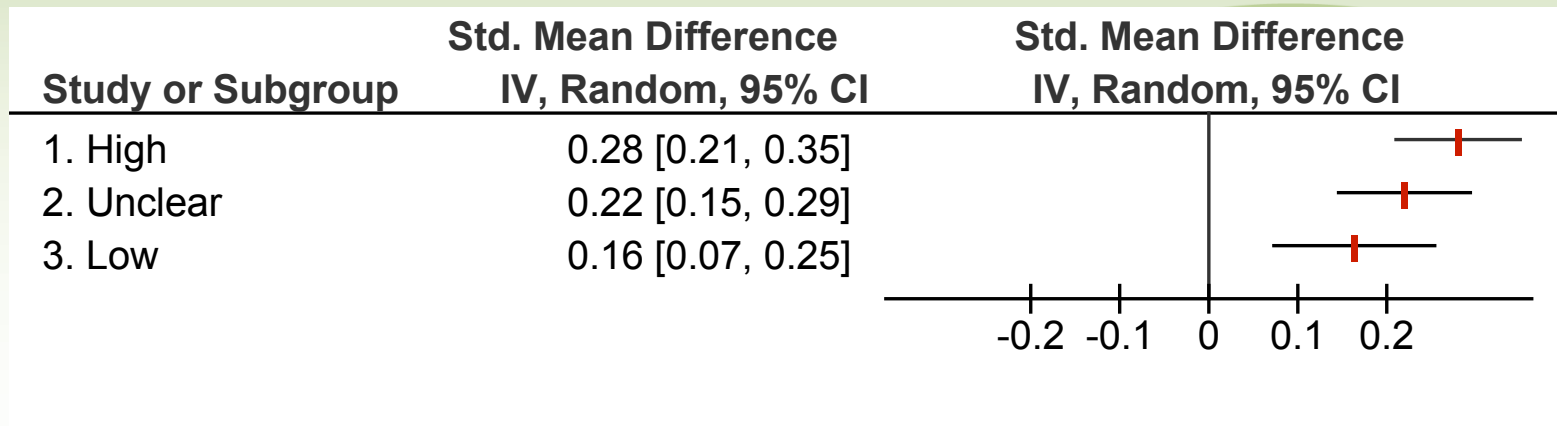
Descriptive Analysis of Pediatric Trials

- *Objectives:* To provide an overview of a representative sample of pediatric RCTs published in 2007 and assess the validity of their results.
- 300 randomly selected RCTs indexed in the Cochrane Central Register of Controlled Trials
- Data extraction:
 - publication and trial characteristics
 - outcomes and conclusions
 - **methodological quality and reporting**
 - trial registration and protocol characteristics

Risk of Bias Assessments by Domain (N=300)

Domain	Risk of bias assessments – n (%)		
	High	Unclear	Low
Sequence generation	8 (2.7%)	143 (47.7%)	149 (49.7%)
Allocation concealment	8 (2.7%)	217 (72.3%)	75 (25.0%)
Blinding	41 (13.7%)	108 (36.0%)	151 (50.3%)
Incomplete data	60 (20.0%)	53 (17.7%)	187 (62.3%)
Selective reporting	48 (16.0%)	6 (2.0%)	246 (82.0%)
Other sources of bias	85 (28.3%)	109 (36.3%)	106 (35.3%)
Overall risk of bias	178 (59.3%)	99 (33.0%)	23 (7.7%)

Effect Sizes and Risk of Bias



Quality of Pediatric Trials

- **Thomson et al:** trends in RCTs from 1948-2006 (*PLoS One* 2010;5:9)
- **Hartling et al:** 163 trials presented as abstracts from 1992-1995 (*BMJ* 2009; 339:b4012)
- **Crocetti et al:** 146 trials published in high impact journals in 2007-2008 (*Pediatrics* 2010; 126(2):298-305)
- **Nor Aripin et al:** 604 pharmacological trials from 2007 (*Paediatr Drugs* 2010; 12(2):99-103)

Survey of Pediatric Trialists

- *Objective:* To determine the barriers and facilitators faced by pediatric trialists in the design, conduct, and reporting of methodologically rigorous trials.

Survey Methods

- Internet-based survey (SurveyMonkey)
- Surveyed corresponding authors of pediatric trials published in 2008 and 2009
 - Entire sample of Canadian researchers (n=90)
 - Random sample of international researchers (n=600)
- Questions to determine:
 - 1) knowledge and awareness of bias
 - 2) perceived barriers and facilitators in conducting trials
 - 3) utility of potential KT strategies for future interventions

Survey Challenges

- 19.9% response rate (128/644; 46 undeliverable)
- SurveyMonkey to REDCap
- Sampled from MICYRN membership (n=163)
- **23.0%** response rate (186/807)

Survey Results

1) Knowledge and awareness of bias

- Identification of bias: responses ranged from Strongly Agree to Strongly Disagree
- Self-rated confidence in understanding of bias: mean 5.4/7

Survey Results

2) Barriers and facilitators

■ **Barriers:**

- Lack of sufficient funding (**70.3%**);
 - Overwhelming volume of literature (**63.1%**);
 - Logistics make it difficult to minimize bias (**52.9%**)
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- *Open-ended responses:* blinding, buy-in from clinicians and organizational leadership

Survey Results

2) Barriers and facilitators

■ **Facilitators:**

- Interest in staying current with literature (**93.0%**);
- Opportunities to discuss methods with knowledgeable colleagues (**92.8%**);
- Rigorous methods encouraged by colleagues (**80.4%**)
- *Open-ended responses:* culture supportive of research, strong collaborators

Survey Results

3) KT strategies

- Checklists or reminders (**90.7%**)
- Online resource centre (**88.7%**)
- Lectures or seminars (**76.7%**)
- Opinion leaders (**73.2%**)
- Educational materials (**62.0%**)

Follow-up Interviews

- *Objective:* To gain greater insight into how researchers' beliefs and values related to working with children and their caregivers intersect with issues of study design.

Interview Methods

- MICYRN survey respondents invited to participate in an interview
- Semi-structured interviews building upon quantitative survey data
- Target sample size of 12 pediatric trialists
- Questions to determine:
 - Relationships between participants' beliefs, behaviours, and attitudes about conducting research on children and appropriate design and conduct of methodologically sound trials

Interview Results

- Ongoing – 4 interviews conducted so far
- **Barriers:**
 - Blinding: type of interventions
 - Logistics: fragmented ethics review system
 - Conflict between clinical care and clinical research
- **Facilitators:**
 - Research networks
 - Positive working relationships – colleagues and sponsors
 - Generating support prior to trial initiation

Future Directions

- *Objectives:* To design and evaluate a tailored KT intervention to improve methodological rigor in child health trials.
- Researcher involvement sought throughout
- Potential interventions: online module, checklists

Future Directions

- StaR Child Health
 - Risk of Bias Standard Development Group
 - Research agenda includes support for knowledge translation initiatives
 - Envision online support and resources for researchers

Discussion

- How do we engage trialists?
 - Reasons for low response rates?
- What is the optimal format for a KT intervention?
- Who is the optimal audience for a KT strategy?
 - Trainees?
 - Established researchers?

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