University of Alberta

Knowledge Translation to Improve Research and Decision-making in Child Health

by

Michele Hamm

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Abstract

Background: Bias is a significant concern in pediatric randomized controlled trials (RCTs), but while there have been numerous calls for improvement in trial conduct, traditional means of education and dissemination of methodological principles have not had a substantial effect on the quality of published research.

Objective: To investigate the use of knowledge translation to address the gap between what is known about clinical trial methodology and how pediatric RCTs are designed and conducted in practice.

Methods: This study was conducted in four phases. To obtain a descriptive overview of the quality of pediatric RCTs, 300 studies published in 2007 were assessed for methodological quality and reporting. A mixed methods study was then conducted with pediatric trialists to identify the barriers and facilitators in conducting methodologically rigorous RCTs. Corresponding authors of 690 pediatric RCTs published in 2008 and 2009 were surveyed and 13 trialists identified through the Maternal Infant Child and Youth Research Network were interviewed. The feedback from the survey and interviews, and a scoping review on the uses of social media by health care professionals led to the development of a wiki-based educational tool. The wiki was pilot tested for usability by conducting interviews with 15 trialists and methodologists.

Results: Most trials from our 2007 sample were at high (59.3%) or unclear (33.0%) risk of bias. Barriers related to conducting methodologically rigorous trials included a lack of knowledge of bias and a negative research culture;

facilitators included supportive colleagues and collaborative working relationships. Ninety six studies were identified in the scoping review, highlighting the prominence of social media in health care education. The use of a wiki as an online resource for providing guidance on minimizing bias was viewed favourably by participants, particularly components that put methodological principles into an applied context, such as case studies and examples.

Conclusions: While methodological limitations in pediatric RCTs persist, a wiki developed to provide guidance on minimizing bias is a promising knowledge translation intervention to increase the quality of research in child health.

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List of Abbreviations

CCCTG: Canadian Critical Care Trials Group

CENTRAL: Cochrane Central Register of Controlled Trials

CI: confidence interval

CONSORT: Consolidated Standards of Reporting Trials

CONSORT-CRT: CONSORT Statement – Extension to Cluster Randomised Trials

EPOC: Effective Practice and Organisation of Care Review Group

HHS: U.S. Department of Health and Human Services

ICMJE: International Committee of Medical Journal Editors

ICTRP: International Clinical Trials Registry Platform

IQR: interquartile range

KT: knowledge translation

MICYRN: Maternal Infant Child and Youth Research Network

OR: odds ratio

PERC: Pediatric Emergency Research Canada

RCT: randomized controlled trial

RD: risk difference

ROB: risk of bias

SD: standard deviation

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

StaR Child Health: Standards for Research in Child Health

UK: United Kingdom

USA: United States of America

WHO: World Health Organization

Chapter 1
Introduction

1.1. Overview of the problem to be addressed

Methodological limitations in the design and conduct of randomized controlled trials (RCTs) are well documented, and the evidence includes a body of literature specific to the gaps in quality in pediatric research. Additionally, trials in child health remain underrepresented relative to adult trials,[1,2] their focus is not necessarily driven by child-relevant issues,[3,4] and their results are often not made available to interested groups.[5,6] These concerns provide a compelling argument that a focus on improving the relevance and methodological rigor in pediatric research is necessary.[7]

Bias is a significant concern in RCTs and there have been numerous calls for improvement in trial conduct.[8,9] Guidance on minimizing bias is available,[10-19] but there is a methods research – research practice gap that has yet to be addressed. Traditional means of education and dissemination of methodological principles have not had a substantial effect on the quality of published research, therefore knowledge translation strategies that seek to act as a bridge between what is known and what is done may offer novel techniques for managing this problem.

The primary aim of this study was to investigate the use of knowledge translation to address the gap between what is known about methodological processes and how pediatric trials are designed and conducted in practice. This work was conducted in four interrelated phases: 1) a description of the quality of recently published RCTs in child health; 2) a mixed-methods evaluation of the barriers and facilitators that pediatric trialists face in the conduct of methodologically rigorous studies; 3) a scoping review of social media tools that have been used in effecting behaviour change in health care professionals and trainees; and 4) the development and evaluation of a wiki-based educational resource for pediatric researchers.

1.2. Literature review

1.2.1. Risk of bias

The introduction of bias into a trial leads to a systematic error in the results, potentially exaggerating or underestimating treatment benefits and/or harms. The risk of bias of a trial is a measure of its internal validity, or the degree to which the results "should be believed."[20] In an extensive compilation of the existing empirical research on the impact of certain design features on treatment effect sizes, The Cochrane Collaboration established a list of seven key domains that are highly influential in the validity of a trial: sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. A classification scheme of these biases is provided in Table 1.1. Substantial evidence exists on the relationship between each of these domains and the introduction of bias into a trial and has been summarized extensively elsewhere.[20-22]

1.2.2. Evaluations of the quality of pediatric trials

There are a number of studies that have evaluated the methodological quality and/or risk of bias of pediatric trials, both in broad overviews of pediatric research and in focused subspecialty areas. While there have been improvements in certain quality measures over time, the evidence uniformly indicates that better research is needed. A summary of the evidence is presented below and in Table 1.2, emphasizing study design features that are included in The Cochrane Collaboration's Risk of Bias tool.

General pediatric reviews

Thomson et al.[23] conducted an analysis of trends in 578 pediatric RCTs published between 1948 and 2006 and found that the proportion of trials that were double-blind and that reported adequate methods of allocation concealment increased

over this period. The mean Jadad score, which addresses issues of randomization, blinding, and study withdrawals,[24] had also increased. However, even in the most recent time period, from 2002 to 2006, 37.7% of trial reports did not describe the level of blinding, 83.0% had unclear or inadequate allocation concealment, and the mean Jadad score was just over two out of a maximum of five.

In a similar evaluation of trends in pediatric RCTs, Campbell et al.[25] extracted data on all trials published in *Archives of Disease in Childhood* between 1982 and 1996 (n=249). Study characteristics related to allocation concealment, incomplete outcome data, and blinding were collected. Over the 15 year study period, the number of trials reporting on these parameters tended to increase; however in trials published between 1992 and 1996, 28% met the highest quality standards for allocation concealment, 31% for completeness of data, and 47% for blinding of outcome assessment.

A systematic review of pediatric drug trials published in 2007 identified 582 RCTs.[26] In this sample, the mean Jadad score was 3.22 (standard deviation 1.31), which is considered to be good quality.[24] All of the included studies were described as randomized, but only 54% described an appropriate method of sequence generation, 53% were double-blind, 49% used an appropriate method of double-blinding, and 67% described withdrawals and dropouts. Quality scores were significantly higher in high and upper-middle income countries than in low and lower-middle income countries (mean 3.27 *vs.* 2.90; p=0.003).

Two studies have been conducted that have used The Cochrane Collaboration's Risk of Bias tool to assess included trials. Hartling et al.[27] examined 163 child health trials presented as abstracts at the annual meetings of the Society for Pediatric Research between 1992 and 1995 and found that 96% were at unclear or high risk of bias. Additionally, effect sizes were higher in trials at high risk of bias than in those at low risk (0.52 [95% CI 0.37, 0.66] *vs.* 0.23 [95% CI -0.16, 0.62]). More recently, a study of 146 pediatric RCTs published in high impact journals in

2007 and 2008 found that 41% of the included studies were judged to be at high or unclear risk of bias for sequence generation and 57% were at high or unclear risk of bias for allocation concealment.[28]

Pediatric subspecialty reviews

Complementary to the evidence describing RCTs in child health as a whole, a series of studies evaluating methodological quality in pediatric subspecialties has also accumulated. In pediatric surgery, Thakur et al.[29] conducted an analysis of all studies published in 1998 in the *Journal of Pediatric Surgery* and *Pediatric Surgery International*. Of 642 published studies, 3 were RCTs. While losses to follow up were reported in all trials, two (66.7%) described the method of randomization and blinding of the patient and one (33.3%) reported blinded outcome assessment. Moss et al.[30] identified 134 surgical RCTs published between 1966 and 1999. The method of randomization was reported in 46% of trials and was adequate in 43%. Patients were blinded in 50% of the studies, whereas the evaluating physician was blinded to the treatment group in only 6% of cases. Curry et al.[31] evaluated a set of more recently conducted surgical trials, assessing abstracts accepted for presentation at the Annual British Association of Paediatric Surgeons Congress between 1996 and 2000. Of 760 abstracts, 9 were RCTs. None of these abstracts specified the method of randomization and only one reported blinding the intervention or outcome measure.

Welk et al.[32] examined 77 RCTs published in pediatric urology between 1966 and 2004. The median Jadad score was 3, and 17% of trials attained a score of 4 or greater. Included studies were separated into surgical and nonsurgical trials, showing that blinding of participants and investigators was more common in nonsurgical trials (68% and 61%, for participants and investigators respectively, *vs.* 21% and 21% in surgical trials), while adequate allocation techniques were more common in surgical trials (35% *vs.* 11%). Overall, adequate allocation was found in 22% of RCTs, blinding of the investigator in 44%, blinding of the participant in 48%, and blinding of the outcome assessor in 13%. Unlike in the

analyses of time trends reported above,[23,25] trial quality in this sample did not show improvement when divided into those published before and after 2000.

Dulai et al.[33] investigated 36 RCTs published in 7 journals with high clinical impact in pediatric orthopedics between 1995 and 2005. Using the Detsky Quality Assessment Scale of RCTs,[34] which assigns a maximum of four points for randomization, the mean score in these trials was 1.94 (95% CI 1.49, 2.39). As in the review of urology studies described above,[32] trials were divided into those evaluating surgical and nonsurgical interventions, and the nonsurgical trials were found to be of higher methodological quality.

Brooks et al.[35] evaluated 27 RCTs in kidney transplant recipients that had enrolled at least 1 child and were published between 2000 and 2008. Nine trials were in exclusively pediatric populations and 18 were mixed pediatric and adult populations; there were no differences in methodological quality between the two groups. Using the 2001 version of the Consolidated Standards of Reporting Trials (CONSORT) Statement[36] as a checklist, the authors found that 37.0% of trials reported the method of sequence generation, 33.3% reported adequate allocation concealment, 7.4% completely reported details of who was blinded, 74.1% reported the flow of participants through the trial, 48.1% used a true intention-to-treat analysis, and 33.3% fully reported all outcomes.

Two studies investigated design characteristics of controlled trials in cystic fibrosis between 1966 and 2002. Cheng et al.[37] reviewed 506 trials published between 1966 and 1997 and found that 36.6% were described as double-blind. In an update of this review, Briggs et al.[38] used the same criteria to assess 261 trials published between 1998 and 2002 and found that the results were essentially unchanged. In the newer set of trials, 32.6% were described as double-blind.

Using a combination of assessment tools, Moher et al.[39] appraised 251 RCTs that evaluated a complementary and alternative medicine intervention in a pediatric

population (study dates not reported). The method of allocation concealment was adequate in 18.7% of trials, according to the framework defined by Schulz et al.[40] The mean score on the two items on the Jadad scale addressing adequate randomization was 0.9 (SD 0.6), and the mean score for the two items addressing an adequate method of double-blinding was 0.6 (SD 0.9).

Anttila et al.[41] used the CONSORT Statement to evaluate 15 RCTs on physiotherapy interventions for cerebral palsy published between 1990 and 2002. Overall, these studies adequately reported on 48.2% of the checklist items, but the features associated with bias were not appropriately addressed. None of the trials described concealment of allocation and only one third described an appropriate method of sequence generation, used an intention-to-treat analysis, or specified the primary outcome. Blinding of the outcome assessors and describing the flow of participants were reported more frequently, in 73.3% of trials.

Abrahamyan et al.[42] used an individual component approach to assess the quality of 52 RCTs in juvenile idiopathic arthritis published between 1966 and 2006. Adequate generation of the allocation sequence was reported in 21.2% of trials, and adequate allocation concealment in 36.5%. Appropriate methods of blinding, including blinding of outcome assessors when blinding of other parties was not possible, was employed in 73.1% of trials. Intention-to-treat analyses were conducted in 37% of studies, although of these 19 trials, only 5 reported how missing data were handled. Half of the included studies clearly specified the primary outcome.

In a review of psychological interventions for pediatric procedural pain (study dates not reported), Uman et al.[43] examined 28 RCTs and found that the majority of the studies failed to meet their criteria for fair to good methodological quality. An appropriate randomization method was reported in 17.9% of cases and no trial reported adequate allocation concealment. The mean proportion of trials satisfying seven criteria on how the study addressed the flow of participants was

25.0%. Outcome assessors were blinded to the study conditions in 54.5% of trials, and analyses were by intention-to-treat in 7.1% of trials.

DeMauro et al.[44] used selected criteria from the 2010 revision of the CONSORT Statement[45] to assess the reporting quality of 179 neonatal and infant RCTs published in 6 high impact journals between 2005 and 2009. These trials largely met the criteria for reporting the number of study participants (99%), the number of participants analyzed (94%), and the result of the *a priori* defined primary outcome (96%); however a description of which members of the study team were blinded was found less commonly (83%), and details on the methods of randomization (59%) and allocation concealment (69%) were not well reported.

Cluster randomized trials come with unique methodological challenges, but many aspects of design are shared with parallel trials. Walleser et al.[46] evaluated 106 cluster randomized trials in child health that were published between 2004 and 2010. Using the CONSORT-CRT checklist, an extension of the CONSORT Statement to guide the reporting of cluster trials,[47] the authors found that 46% of trials reported the method of sequence generation and 20% reported the method used to implement the sequence. Fewer than half of the studies reported whether participants (42%), those delivering the intervention (37%), and outcome assessors (45%) were blinded.

Summary

The 19 studies evaluating the methodological quality of pediatric RCTs have used a diverse set of assessment tools, but overwhelmingly and consistently, the evidence suggests that these trials are vulnerable to bias. While each of these studies is bound by the limitation of relying upon the reporting, and not the conduct, of the original trials, low quality of reporting has been associated with exaggerated effect estimates.[27,40] Given the plethora of evidence on conducting methodologically rigorous RCTs and on the poor quality of trials conducted in

pediatrics, research must now turn to methods of ensuring that pediatric trialists are in a position to conduct high quality research.

1.2.3. Knowledge translation in health care professional behaviour change

Methodological and practical challenges are inherent in research in children; therefore it is necessary that the relevant knowledge be translated into guidance for end-users.[48] The science of knowledge translation (KT) seeks to bridge the gap between research (what we know) and practice (what we do). The study of translation of methodological research findings to researchers, and specifically to trialists, is limited, and has so far focused on the impact of reporting guidelines and trial registration.[49,50] However, the knowledge base around changing the behaviour of health care professionals is more extensive, both in terms of the theoretical basis for change and the evaluation of the effectiveness of interventions.

Theoretical Foundation

Knowledge translation theory is constantly evolving and draws on the experience of many other disciplines, including sociology, cognitive psychology, adult education, and organizational culture.[51] While the necessity of the use of theory in KT is debated,[52,53] it is generally held that theory can be advantageous in informing the development of useful and testable interventions.[54,55]

Much research in KT stems from the theory of Diffusion of Innovations,[56] a classical (i.e., descriptive) theory used to explain change. In this model, the determinants of the spread of a new idea are the characteristics of the innovation, communication channels, time, and social system. At the individual level, progression occurs through five stages: awareness, persuasion, decision, implementation, and adoption. While this theory does not explain why changes in behaviour may occur, it provides an outline of considerations that can guide the development of an effective intervention. In contrast to the classical theories of change, planned action theories are intended to predict how behaviour change will

occur.[57] Graham et al.[58] undertook a search of the social sciences, education, management, and health sciences literature, identifying 31 planned action theories intended to guide practice, research, and theory. Arising out of this search were six major factors to consider when implementing change: 1) the nature of the evidence or knowledge; 2) the attributes of the change or innovation; 3) the target audience; 4) the organizational context and culture in which the change is to take place; 5) the organizational resources and support for the proposed change; and 6) implementation-related factors. The compilation of these six elements led to the development of the knowledge-to-action framework that is widely used to guide the progression from knowledge creation and synthesis to dissemination and implementation.[59]

Cognitive psychology theories of change are centered on changing knowledge, attitudes, and beliefs and therefore have been used to guide interventions that may influence individual behaviour.[60] Categories of theories that have been influential in KT include those related to motivation (e.g., social cognitive theory,[61] theory of planned behaviour[62]), action (e.g., implementation intentions,[63] theory of operant conditioning[64]), stages of change (e.g., transtheoretical model of change[65]), and decision making (e.g., cognitive continuum theory[66]). Given the considerable overlap in the constructs proposed in these theories, Michie et al.[67] endeavoured to develop a consensus on a theoretical framework that could be used to study and to develop effective strategies for the implementation of evidence-based practice. An expert panel of health psychology theorists, health services researchers, and health psychologists was assembled to identify and evaluate theoretical domains and to validate the list. Of 128 explanatory domains that were identified, 12 key constructs to explain behaviour change were retained: 1) knowledge; 2) skills; 3) social/professional role and identity (self-standards); 4) beliefs about capabilities (self-efficacy); 5) beliefs about consequences (anticipated outcomes/attitude); 6) motivation and goals (intention); 7) memory, attention, and decision processes; 8) environmental context and resources (environmental constraints); 9) social

influences (norms); 10) emotion; 11) behavioural regulation; and 12) nature of the behaviours.

Educational theories are divided into behaviourist, cognitivist, constructivist, humanist, and social learning approaches and can be used to explain and evaluate the effectiveness of educational interventions. While the theoretical foundation in this area is strong, there is little evidence to validate the underlying assumptions of educational theories.[68]

Organizational theory is relevant to KT as many interventions are either directed at the organizational level or target individual behaviour that is highly influenced by the organizational context. A prolific theory is one developed by Schein, in which observable artifacts, values, and basic underlying assumptions are used to define organizational culture.[69] Further, he suggests that understanding an organization depends on understanding both its ability to adapt to the external environment and the development and maintenance of internal relationships among its members. These, in turn, are influenced by deeper cultural assumptions related to the nature of reality and truth, time, space, human nature, human activity, and human relationships.

Intervention Strategies

The Effective Practice and Organisation of Care (EPOC) Review Group within The Cochrane Collaboration has been instrumental in synthesizing the evidence evaluating the effectiveness of interventions aimed at improving the delivery, practice, and organization of health services.[70] One of their areas of focus has been on continuing education and quality assurance, and an overview of the major types of interventions is provided in Table 1.3. Of particular note for their potential relevance to targeting researcher behaviour are strategies for distribution of educational materials and educational meetings, and the impact of local opinion leaders.

Printed educational materials are the foundation for disseminating research findings in the academic community. Farmer et al.[71] investigated the effectiveness of printed educational materials on process outcomes related to the behaviour of health care professionals in a systematic review of 23 studies and found slight beneficial effects. Comparing printed educational materials to no intervention, a median absolute risk difference (RD) of 4.3% in categorical outcomes was observed (range: -8.0% to 9.6%; six RCTs), along with a 13.6% relative RD in continuous outcomes (range: -5.0% to 26.6%; four RCTs).

Similarly, educational meetings are a mainstay of continuing education and professional development. Forsetlund et al.[72] reviewed 81 trials evaluating professionals' compliance with desired practice and found that overall, effects were small. For studies in which educational meetings were evaluated alone (21 comparisons in 19 trials), or as a component of an intervention (36 comparisons in 30 trials), the median adjusted RD in compliance was 6% versus no intervention. However, meetings that incorporated both didactic and interactive content (RD 13.6%) were more effective than those that presented either didactic (RD 6.9%) or interactive (RD 3.0%) content alone.

The ability of opinion leaders to influence professional practice by disseminating and implementing 'best evidence' was examined in a review of 18 trials.[73] The median adjusted RD for outcomes measuring compliance with desired practice was 9% for opinion leaders compared to no intervention, 14% for opinion leaders alone compared to a single intervention, 10% for opinion leaders with one or more additional interventions compared to the additional intervention(s), and 10% for opinion leaders as part of multiple interventions compared to no intervention. Across all included studies, the median adjusted RD for compliance with desired behaviour was an increase of 12%.

Regardless of the type of intervention used, it is commonly believed that identifying barriers to change and using these to inform the development and

implementation of the intervention will increase its effectiveness. Baker et al.[74] conducted a systematic review of 26 RCTs that evaluated the impact of a tailored intervention compared to no intervention or to an intervention that had not been tailored to address barriers. Twelve studies were included in a meta-regression and contributed to a pooled odds ratio of 1.54 (95% CI 1.16, 2.01), indicating that tailored interventions were more likely to change behaviour than no intervention or dissemination of educational materials or guidelines.

Summary

Knowledge translation involves a complex interaction between individual, organizational, and intervention level factors. Effecting behaviour change must occur in the context of these often competing forces which can be highly variable between settings. An understanding of the theoretical constructs underlying behaviour change and allowing for flexibility in the intervention used can facilitate the dissemination of information, but neither guarantees the uptake of a new idea or innovation. This is supported by the evidence accumulated by the EPOC Review Group, in which the effects of KT interventions range from slight to modest, and typically do not exceed a change in behaviour of more than 10% (Table 1.3).

While research to date has focused on clinician or patient behaviour change, the principles underlying strategies to influence professional behaviour can likely be adapted and applied to researchers. Although the behaviour of interest differs between clinicians (delivery of care) and researchers (conduct of clinical trials), the ultimate goal of improving health-related outcomes is the same. Therefore, the knowledge base that has developed around KT in health care professionals provides an appropriate starting point for investigating the dissemination of methodological guidance for researchers and clinician-scientists.

1.3. Study rationale

This project will contribute to the understanding of challenges faced by trialists in the process of conducting rigorous pediatric research. Well-designed trials play a key role in evidence-based medicine. The uptake of methodological principles by researchers is therefore essential to ensuring that valid research results inform clinical decision-making, ultimately improving patient outcomes. This research program is novel in its focus on researchers, rather than on clinical decision-makers, and will thus advance the science of knowledge translation for this particular end-user group.

1.4. Research question and objectives

The research question guiding this study was: How can knowledge translation be used to improve research and decision-making in child health?

The objectives of this study were to: 1) describe the characteristics and quality of a representative sample of pediatric randomized controlled trials; 2) determine the barriers and facilitators that influence the conduct of pediatric research; and 3) develop and pilot test a knowledge translation intervention to provide methodological guidance to pediatric trialists (Appendix A).

Table 1.1. A common classification scheme for bias

Type of bias	Description	Relevant domains in The Cochrane Collaboration's Risk of Bias tool
Selection bias	Systematic differences between baseline characteristics of the groups that are compared.	▪ Sequence generation ▪ Allocation concealment
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	▪ Blinding of participants and personnel ▪ Other potential threats to validity
Detection bias	Systematic differences between groups in how outcomes are determined.	▪ Blinding of outcome assessment ▪ Other potential threats to validity
Attrition bias	Systematic differences between groups in withdrawals from a study.	▪ Incomplete outcome data
Reporting bias	Systematic differences between reported and unreported findings.	▪ Selective outcome reporting

From: Higgins JPT, Green S, (Eds). Cochrane handbook for systematic reviews of interventions version 5.1.0 (Table 8.4a). Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org.

Table 1.2. Summary of the empirical evidence describing the methodological quality of pediatric trials

				Percentage of trials appropriately addressing domain					
Study	**Pediatric subspecialty**	**Years of publication of included trials**	**n**	**Sequence generation**	**Allocation concealment**	**Blinding – Participants and Personnel**	**Blinding – Outcome Assessors**	**Incomplete outcome data or ITT analysis**	**Selective outcome reporting or specification of primary outcome**
Thomson, 2010[23]	General	2002 – 2006	50	95.3%	17.0%	46.0%*	NR	NR	NR
Campbell, 1998[25]	General	1982 – 1996	249	NR	21.3%	NR	38.6%	41.4%†	NR
Nor Aripin, 2010[26]	Drug trials	2007	582	54.3%	NR	48.4%*	NR	67.2%	NR
Hartling, 2010[27]	General	1992 – 1995[∫]	163	31.9%	32.5%	60.1%	NR	52.8%	78.5%
Crocetti, 2010[28]	General	2007 – 2008	146	58.9%	43.2%	80.8%	NR	89.0%	97.9%
Thakur, 2001[29]	Surgery	1998	3	66.7%	NR	66.7%	33.3%	100%	NR
Moss, 2001[30]	Surgery	1966 – 1999	134	43.3%	NR	50%	6%	25.7%	NR
Curry, 2003[31]	Surgery	1996 – 2000[∫]	9	0%	NR	11.1%	11.1%	NR	NR
Welk, 2006[32]	Urology	1966 – 2004	77	22%	NR	48% (participants); 44% (investigators)	13%	NR	NR
Dulai, 2007[33]	Orthopedics	1995 – 2005	36	mean 1.94/4 (95% CI 1.49, 2.39)	NR	NR	NR	NR	NR
Brooks, 2010[35]	Kidney transplantation	2000 – 2008	27	37.0%	33.3%	7.4%‡	NR	74.1% (participant flow); 48.1%	33.3%

								(ITT)	
Cheng, 2000[37]	Cystic fibrosis	1966 – 1997	506	NR	NR	36.6%*	NR	NR	NR
Briggs, 2006[38]	Cystic fibrosis	1998 – 2002	261	NR	NR	32.6%*	NR	NR	NR
Moher, 2002[39]	Complementary and alternative medicine	NR	251	mean 0.9/2 (SD 0.6)	18.7%	mean 0.6/2 (SD 0.9)*	NR	NR	NR
Anttila, 2006[41]	Cerebral palsy	1990 – 2002	15	33.3%	0%	0%	73.3%	73.3% (participant flow); 33.3% (ITT)	33.3%
Abrahamyan, 2008[42]	Juvenile idiopathic arthritis	1966 – 2006	52	21.2%	36.5%	73.1%*‡	NR	36.5%	50.0%
Uman, 2010[43]	Procedural pain	NR	28	17.9%	0%	NR	54.5%	range of criteria: 3.6% – 67.9%	NR
DeMauro, 2011[44]	Neonatology	2005 – 2009	179	59.2%	68.7%	83.5%‡	NR	range of criteria: 49.7% – 98.9%	79.3%
Walleser, 2011[46]	Cluster randomized trials	2004 – 2010	106	46.2%	18.9%	42.5% (participants); 36.8% (investigators)	45.3%	range of criteria: 25.5% – 84.0%	62.3%

NR: not reported; ITT: intention to treat; 95% CI: 95% confidence interval; SD: standard deviation; [] presented as abstracts; *double-blind; †completeness of data in primary analysis; ‡combines participants and personnel with outcome assessors

Table 1.3. EPOC framework of knowledge translation interventions

Intervention type	Review	Comparison	Results*
Audit and feedback	Ivers, 2012 [75] (140 studies)	Audit and feedback *vs.* usual care	Dichotomous outcomes: 4.3% (IQR 0.5% to 16%) Continuous outcomes: 1.3% (IQR 1.3% to 28.9%)
Distribution of educational materials	Farmer, 2008[71] (23 studies)	Printed educational materials *vs.* no intervention	Categorical outcomes: 4.3% (range -8.0% to 9.6%) Continuous outcomes: 13.6% (range -5.0% to 26.6%) relative risk difference
Educational meetings	Forsetlund, 2009[72] (81 studies)	Educational meetings *vs.* no intervention	Mixed interactive and didactic meetings: 13.6% Didactic meetings: 6.9% Interactive meetings: 3.0%
Educational outreach visits	O'Brien, 2007[76] (69 studies)	Educational meetings *vs.* no intervention	5.6% (IQR 3.0% to 9.0%)
Local opinion leaders	Flodgren, 2011[73] (18 studies)	Opinion leaders *vs.* no intervention, a single intervention, or multiple interventions	12% (range 6.0% to 14.5%)
Mass media	Grilli, 2002[77] (20 studies)	Mass media *vs.* control	No numeric data
Other	Baker, 2010[74] (26 studies)	Tailored interventions *vs.* no intervention or an intervention(s) not tailored to barriers	Pooled odds ratio 1.54 (95% CI 1.16, 2.01)
	Reeves, 2008[78] (6 studies)	Interprofessional education *vs.* separated education interventions	No numeric data
Reminders	Shojania, 2009[79] (28 studies)	On-screen, point of care computer reminders *vs.* control	4.2% (IQR 0.8% to 18.8%)

*Median adjusted risk difference in compliance with desired practice (absolute increase), unless otherwise specified. IQR: interquartile range; 95% CI: 95% confidence interval.

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Chapter 2

A descriptive analysis of a representative sample of pediatric randomized controlled trials published in 2007[1]

Michele P Hamm, Lisa Hartling, Andrea Milne, Lisa Tjosvold, Ben Vandermeer, Denise Thomson, Sarah Curtis, Terry P Klassen

2.1. Background

Randomized controlled trials (RCTs) are considered the gold standard for research on therapeutic interventions and provide the best evidence to inform and guide clinical decision-making. Currently the number of pediatric trials conducted and published lags behind that for adults.[1,2] In addition, little is known about the risk of bias, or validity, of pediatric RCTs.

Substantial evidence demonstrates that particular study design features increase the likelihood of systematic error, or bias, most often resulting in over-estimation of treatment effects. Risk of bias (ROB) reflects the degree to which the results of a trial should be believed.[3] Building on previous research around methodological quality of RCTs,[4,5] The Cochrane Collaboration recently introduced a tool designed to appraise ROB, encompassing six domains related to the internal validity of a trial: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" potential threats to validity.[3]

Recent initiatives to address some of the biases associated with the design, conduct, and reporting of trials include the International Committee of Medical Journal Editors' (ICMJE) statement on trial registration[6] and reporting guidelines (www.equator-network.org) such as the CONSORT Statement (Consolidated Standards of Reporting Trials).[7] Trial registration is integral in addressing the bias

[1] *A version of this chapter has been published. Hamm et al. BMC Pediatrics 2010; 10:96. The BioMed Central copyright and license agreement is available in Appendix B.*

associated with selective outcome reporting by ensuring that investigators prospectively provide details on their trial, allowing for increased transparency and accountability.[8] The CONSORT Statement was developed to ensure adequate and transparent reporting upon completion of the trial and comprises a checklist of items that should be included in the publication of any RCT. Evidence suggests that these strategies have positively influenced the quality of published trials,[9-11] but this has yet to be assessed in pediatrics.

Given these recent initiatives to improve reporting and assess ROB, we aimed to describe the state of pediatric evidence using a representative sample of child health RCTs published in 2007. Specific objectives were to examine: 1) methodological quality, including ROB, and its association with effect estimates; 2) the rate of trial registration and author reasons for registration and non-registration; and, 3) availability of trial protocols and their consistency with publications.

2.2. Methods

2.2.1. Sample selection

Using a pediatric filter, the Cochrane Central Register of Controlled Trials (CENTRAL) was searched for trials published in 2007 (Appendix C).[12] CENTRAL is comprised of records of studies indexed in Medline and Embase, as well as hand-search results, grey literature, and the trials registers of Cochrane Review Groups.[13] As such, this provided a thorough search for pediatric controlled trials. Two thousand eight hundred thirty-two trials were randomly ordered using a computer-generated list, were screened consecutively for relevance, and the first 300 (approximately 10%) RCTs matching the criteria below were selected. Trials were included if they were published in English and included participants aged 0 to 18 years. If a trial studied both children and adults, it was included if the upper age limit was ≤21 years.[13]

2.2.2. Data extraction

Data were extracted on: publication (e.g., type of journal, impact factor) and trial characteristics; outcomes and conclusions; methodological quality and reporting; and trial registration and protocol characteristics related to outcomes (Appendix D). Data extraction was completed by one reviewer with an independent second review on a randomly selected 10% sample. Discrepancies were resolved through consensus and were negligible. Trial registration and protocol availability were determined for each study based on publication details, an Internet search, and author follow-up.

2.2.3. Assessment of methodological quality and reporting

Given the range of quality assessment methods available, and the widespread use of many, methodological quality and reporting were assessed using multiple tools: the Jadad scale[4] and allocation concealment,[5] as well as the Cochrane ROB tool[3] and the 2001 CONSORT Statement.[14] The Jadad scale is a five-point scale based on the description of randomization, double-blinding, and withdrawals or losses to follow-up; a score of 5 indicates highest quality. Allocation concealment was assessed as adequate, inadequate, or unclear. Nearly all trials in our sample were efficacy trials; therefore we focused on the original CONSORT Statement. The 2001 CONSORT checklist was the most recently published version at the time of data extraction, and assesses reporting with respect to 22 items. Each item was assessed as fully, partially, or not met.

The ROB tool was applied based on guidelines established by The Cochrane Collaboration,[3] with some modifications specific to our investigation (Appendix E). These consist of decision rules that have been developed by our centre that have been used in conjunction with the Cochrane guidelines to increase consistency across reviewers. An overall assessment of ROB was made as high, low, or unclear based on the criteria from the Cochrane handbook: if any of the six domains were judged to be at high risk of bias, the overall risk was considered high; if any were judged to be at unclear risk of bias and none at high risk, the overall risk was unclear; and if all six domains were judged to be at low risk of

bias, the overall risk was low. The tool was pilot tested by all members of the study team. Trials were assessed independently by two trained reviewers who arrived at consensus for each of the six items.

2.2.4. Trial registration and protocol availability

To determine whether or not trials were registered, details were first sought in the publication. If a declaration was not made, we searched through the International Clinical Trials Registry Platform (ICTRP) search portal maintained by the World Health Organization (WHO). If not found, the following registries were searched in order: ClinicalStudyResults.org, Memorial Sloan-Kettering Cancer Center, Current Controlled Trials Meta-Register, and CenterWatch. While there was some overlap in registries searched (i.e. ISRCTN.org is included in both the ICTRP portal and the Current Controlled Trials Meta-Register), each register contained unique databases. If a trial was not found in any of these registries, we conducted a Google search using the names of the first, last, and/or corresponding authors and key words. When available, data from the registry or from protocols found in our search were compared to the publication.

A 28-question survey regarding trial registration and protocol availability was sent to all corresponding authors with current email contact information (n=290; Appendix F). The initial invitation and survey link was followed by two reminders containing the same information. Protocols were requested from authors. Ethical approval was obtained from the Health Research Ethics Board at the University of Alberta prior to survey implementation.

2.2.5. Analysis

Data were analyzed descriptively, using means and standard deviations or medians and ranges for continuous variables and proportions for categorical variables. Effect sizes were computed for 236 trials with sufficient data based on the primary outcome for that trial. The effect size was a standardized mean difference when the primary outcome was continuous and a converted odds ratio

when dichotomous.[15] Effect sizes were pooled using DerSimonian-Laird random effects for each of the three ROB categories (high, low, unclear). To compare ROB for certain covariates, a reference category was chosen within each variable classification and odds ratios comparing the number of high/unclear risk trials to low risk trials were computed with 95% confidence intervals.

2.3. Results

2.3.1. Description of study sample

Publication and trial characteristics of our sample of 300 trials are shown in Table 2.1. The majority of trials used parallel designs (89.7%), were efficacy trials (82.7%), and were published in specialty journals (78.6%). Evaluation of pharmacological interventions was most common (40.3%) and 30% of trials were placebo-controlled. While all major geographic areas were represented, the majority of authors were from Europe (40.3%) and North America (29.0%). Each study was categorized using the review groups of The Cochrane Collaboration: neonatal (9.3%), oral health (7.7%), and developmental, psychosocial, and learning problems (6.7%) were most represented.

2.3.2. Methodological quality

The median Jadad score was 2 (IQR 2-3). Allocation concealment was adequate in 21.7% of trials, while 75.7% were unclear (Table 2.2). Only three trials (1.0%) sufficiently addressed all 22 items of the CONSORT Statement (IQR 13-17) with another eight (2.7%) at least partially meeting all requirements (IQR 15-19). The remaining 289 trials (96.3%) failed to report at least one, and up to 14 recommended items. Overall, the median number of items that were adequately addressed was 15, and five for those partially addressed. Descriptions of the "method used to implement the randomization sequence" (item 9) and "who generated the allocation sequence and enrolled and assigned participants" (item 10) were the most under-reported, with 214 (71.3%) and 229 (76.3%) trials not meeting these criteria respectively.

Overall ROB was low for 23 trials (7.7%), unclear for 99 (33.0%), and high for 178 (59.3%) (Table 2.2). Much of the uncertainty in rating studies was due to unclear reporting. Selective outcome reporting was rated as low ROB in nearly all trials. "Other" sources of bias included inappropriate influence of the study sponsor (e.g. industry funding without separation from the conduct of the trial), imbalance in baseline characteristics, and design-specific issues (e.g., factors related to cluster RCTs or cross-over trials), and was the domain that was least often addressed satisfactorily (Table 2.3). Trials at low ROB had higher mean Jadad scores and were more likely to report adequate means of allocation concealment than those at high ROB (Table 2.4).

Effect sizes tended to increase from studies at low (0.16, 95% CI 0.07,0.25) to high ROB (0.28, 95% CI 0.21,0.35; p=0.051; Figure 2.1).

Each of the ROB domains and the overall ratings were examined in the context of the following variables: trial registration, industry funding, multi-centre status, number of treatment arms, intervention type, primary outcome category, and type of journal (Appendix G). Of these variables, trial registration had the most influence on ROB. Compared to trials that were not registered, those trials that were had a lower overall ROB, as well as a lower ROB for each of the domains except selective outcome reporting. Odds ratios for high ROB ranged from 0.29 (95% CI 0.12,0.69) for overall ROB to 0.47 (95% CI 0.27,0.81) for "other" sources of bias. Trials that were sponsored by industry were more likely to have adequate blinding than non-industry funded trials (OR 0.41 (95% CI 0.22,0.76)), but were also more likely to be associated with "other" sources of bias (OR 4.72 (95% CI 2.46,9.07)). ROB for selective outcome reporting increased with number of arms in the trial (p=0.007), but was unchanged for the other domains. When compared to pharmacological interventions, trials investigating devices had a higher ROB associated with blinding (OR 3.37 (95% CI 1.62,7.02)) and incomplete data (OR 2.56 (95% CI 1.26,5.21)). High ROB due to blinding was also found in studies with outcomes related to techniques/training (e.g., longevity

of dental restorations) when compared to physiological outcomes (OR 5.28 (95% CI 1.09,25.61)). Multi-centre status and type of journal had no impact on ROB.

Trial registration was declared in the publication of 37 trials (12.3%) and 69 records of registration (23.0%) were found online. Registered trials were more likely to be published in journals with a higher impact factor (median 4.017 *vs.* 1.883; $p<0.0001$). Approximately one third of trials were registered in studies with corresponding authors from Africa (36.4%), North and South America (34.5% and 28.6%, respectively), and the UK (30.0%), but proportions were lower for the rest of Europe (18.7%), Asia (10.3%), and Australia (6.3%). Registered trials more often specified their funding source (89.9% vs. 57.1%; $p<0.0001$), and less often reported statistically significant findings, although this comparison was not statistically significant (68.1% *vs.* 79.2%; $p=0.07$). Measures of methodological quality were superior in registered trials (Table 2.4).

2.3.3. Author follow-up survey

145 authors (50.0%) responded to the survey, therefore the ability to generalize findings is limited. Of respondents, 61 (42.4%) reported registration with a public trial registry, potentially corresponding closely to the 69 found in our search. The majority of these were registered with ClinicalTrials.gov (67.5%) or Current Controlled Trials (17.5%). 51.2% were registered prior to and 37.2% after patient recruitment. The most common reason for registering a trial was a journal requirement for publication (72.7%), followed by a belief in full public disclosure (68.2%). For non-registration, the most common reasons were lack of familiarity with the process (59.1%) and trial initiation prior to registration endorsement by the ICMJE (51.5%) (Table 2.5).

Nearly all respondents (92.2%) had prepared a study protocol prior to trial initiation; 2.0% reported a minor difference between the protocol and study conduct. 9.7% of authors reported that some outcomes measured in the trial were not reported in the publication. Space limitations were the most common concern

(journal imposed space limitation 41.7%; authors' concern about space 25.0%), followed by non-statistically significant findings (41.7%). While 56.4% of respondents indicated that they were willing to share their protocol, only two were received. In both cases, the details in the publication were consistent with the protocol.

2.4. Discussion

Our sample of recently-published pediatric trials demonstrates that there is considerable room for improvement in their design, conduct, and reporting. Methodological quality was modest, with the vast majority of trials at high or unclear ROB. Further, the trials did not adhere to widely accepted reporting standards or requirements for trial registration.

Our sample was intended to be representative of all RCTs published in 2007; therefore we placed no restrictions on journal, clinical area, or type of intervention. Trials in our sample were largely published in specialty journals, and examined a variety of interventions among a diverse range of conditions.

Methodological quality was assessed using three well-recognized tools and the results overall were not favorable, suggesting methodological weaknesses and high risk of bias. Incomplete reporting was prevalent; while statements declaring implementation of certain design features (e.g., randomization and "double-blinding") were common, detailed methods were often not specified. Further, allocation concealment was rarely addressed at all. Despite the differing emphasis of the tools used (i.e., conduct for ROB and quality of reporting for Jadad and CONSORT), the results were consistent in that overall, the trials did not meet the criteria of any of the methods of assessment. However, there is evidence to suggest that the Jadad scale and ROB measure different constructs and that the assessment of ROB may be more appropriate.[16]

Selective outcome reporting is of great concern. It is one of the driving forces for the promotion of trial registration and has important implications for safety.[17-20] To assess this domain, we compared the outcomes specified in the protocol or in the trial register to those reported in the publication; however the lack of registered trials and the extremely low response to requests for protocols made this difficult. As a result, our findings likely underestimate the risk associated with this particular issue, as we were unable to assess potential biases introduced through discrepancies between the original trial design and actual conduct.

Evidence suggests that industry-funded trials are more likely to report favorable results,[21-23] therefore we included a criterion within the "other" sources of bias domain that related to inappropriate influence of the funding body. Provided that the source of funding was declared and a statement was made outlining the role of the sponsor, we considered the trial to be low ROB for that measure; however this information was often missing. While funding source was not the only consideration in assessing "other" sources of bias, it was relevant to every trial, and was therefore important in the determination of our overall results showing high or unclear ROB for this domain among two thirds of trials.

We found a noteworthy trend toward increasing effect estimates with increasing ROB which is consistent with previous research.[16] Trials at high ROB had a larger mean effect size than trials at low ROB, indicating the potential for a high proportion of trials to be reporting exaggerated results. These results are exploratory and should be interpreted with caution given the heterogeneity in outcomes compared and the small number of studies. Further work and methods that better account for confounding due to intervention and diagnostic condition are required before firm conclusions can be made.

Despite wide support,[24] uptake by journals of the CONSORT Statement has been variable. In a survey of 165 high impact journals in 2007, 38% mentioned the CONSORT Statement in the instructions to authors and 14% required (rather than

recommended) it to be completed for a trial to be accepted.[25] This variability is echoed in our sample, as very few trials met all of the requirements of the checklist. Of the 11 trials that at least partially met all requirements, nine journals were represented. Of these, two journals stated in their instructions to authors that a completed CONSORT checklist was required, three recommended following the CONSORT guidelines, and the remainder did not mention the CONSORT Statement. Our observation that journal endorsement of the CONSORT Statement has little bearing on whether all of the recommended elements are reported highlights the practical issue of how to ensure adherence to the guidelines, and ultimately their impact on reporting.

Very few trials in our sample were registered in a public registry, and only about half of those that were registered declared this in the publication. Prospective trial registration has been heavily endorsed, and the volume of trials registered appears to be increasing.[26-28] However, trial registration is far from universal, and is perhaps more problematic in pediatric trials. Pandolfini and Bonati[29] found that the proportion of pediatric trials among all registered trials in online registers was disproportionate to those in the published literature. Pediatric trials are more likely to be published in specialty journals which may be less likely to require trial registration than general medical journals. Another concern is that the requirement for trial registration may not be enforced. Our author survey suggests that one of the major barriers to trial registration among respondents is a lack of familiarity with the process; therefore, efforts are required to raise awareness. These efforts should target researchers at the study design stage, rather than at the point of publication. However, reluctance on the part of academic researchers to publicly disclose the information required by trial registers may pose a challenge,[30] an issue that was reinforced in this study by the apparent futility of contacting authors for access to protocol data. Potential future directions in this area may include the requirement of publicly available protocols at the time of trial registration or with funding applications.

Based on our findings, there is clearly room for improvement in pediatric trials. This is the mission of StaR Child Health (Standards for Research in Child Health), an international group that was recently formed involving varied stakeholders to develop and promote guidance to ensure the validity and relevance of pediatric trials.[31] With the involvement of trialists, clinicians, regulators, editors, and representatives of the pharmaceutical industry, this initiative is invested in meeting the needs of the research and clinical communities.[32] Through the development of standards for research in priority areas for pediatric research (e.g. appropriate outcome selection, data and safety monitoring committees, sample size, ROB), StaR Child Health aims to be an important contributor to a methodologically strong evidence base for pediatric care.[33]

2.5. Limitations

We included approximately 10% of pediatric RCTs published in 2007, potentially limiting representativeness. Only trials published in English were included, possibly contributing to the high proportion of studies from North America and the UK. While we extracted the country of the corresponding author, this is not a perfect proxy for the population studied and in some cases, an author from a high income country reported on a trial conducted in a low or middle income area.

The true ROB was often difficult to interpret in our sample due to poor reporting. Additionally, the issue of selective outcome reporting posed a challenge as protocols or trial registers were unavailable for the majority of studies. In most cases, the publication was judged according to its internal consistency. Hence, the high proportion of trials that were given a rating of low ROB for this domain likely underestimates the true ROB.

The pooled analysis presented to examine trends in effect sizes and ROB is preliminary work. Given the heterogeneity in diseases, interventions, and outcomes included in the sample, we used standardized measures of effect size to

be able to investigate general patterns across studies, but these results are exploratory.

The response to our author survey was likely subject to response bias. The item responses indicate that authors who had registered their trials were more likely to participate in the survey, potentially limiting applicability. Assuming that respondents were more aware of issues related to trial registration and methodological initiatives in general, the answers provided (for example reasons for non-registration) may not encompass some of the deeper issues faced by other researchers and may have implications for attempts to overcome these barriers in the future.

2.6. Conclusions

This study shows that the majority of pediatric trials published in 2007 were at high risk of bias, corresponding with a trend toward increased effect sizes. In spite of a movement towards improving methodological quality and requirements for trial registration, the majority of trials have not met these recommendations. These results should be of great concern for child health providers, researchers, methodologists, and funders, and should motivate all to work towards improving the design, conduct, and reporting of child health research.

2.7. Acknowledgements

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Table 2.1. Publication and trial characteristics (N=300)

Study Characteristic	N (%)
Continent of corresponding author	
Africa	11 (3.7)
Asia	58 (19.3)
Australia	16 (5.3)
Europe (excluding UK)	91 (30.3)
North America	87 (29.0)
South America	7 (2.3)
United Kingdom	30 (10.0)
Type of journal	
General medical journal	19 (6.3)
Specialty medical journal	166 (55.3)
General pediatric journal	45 (15.0)
Specialty pediatric journal	70 (23.3)
Study design	
RCT parallel	269 (89.7)
RCT crossover	19 (6.3)
RCT factorial	5 (1.7)
Other	7 (2.3)
Study type	
Efficacy/Superiority	248 (82.7)
Equivalence	9 (3.0)
Non-inferiority	13 (4.3)
Not declared	2 (0.7)
None of the above	25 (8.3)
Unclear	3 (1.0)
Nature of intervention	
Drug	121 (40.3)
Vaccine	16 (5.3)
Natural health product	26 (8.7)
Device	44 (14.7)
Other	93 (31.0)
Placebo-controlled	90 (30.0)
Number of centres	
Multicentre	105 (35.0)
Single Centre	179 (59.7)
Unclear	16 (5.3)
Sample size	
Mean (SD)	785.2 (5837.3)
Median (range), IQR	83 (6 – 71,799), 10 – 7079
Data Monitoring Committee established	14 (4.7)
Any adverse events reported	129 (43.0)

Funding source	
Declared	194 (64.7)
Industry Sponsored	67/194 (34.5)
Primary outcome explicitly reported	123 (41.0)
At least one statistically significant outcome	230 (76.7)
Intervention favoured	
Treatment	189 (63.0)
Control	19 (6.3)
Neither	92 (30.7)
Common primary diagnostic categories	
Acute Respiratory Infections	17 (5.7)
Airways	14 (4.7)
Anaesthesia	18 (6.0)
Developmental, Psychosocial, and Learning Problems	20 (6.7)
Ear, Nose, and Throat Disorders	10 (3.3)
Infectious Disease	19 (6.3)
Metabolic and Endocrine Disorders	15 (5.0)
Neonatal	28 (9.3)
Oral Health	23 (7.7)
Public Health	16 (5.3)

Table 2.2. Assessments of methodological quality (N=300)

Methodological Quality Indicator	N (%)
Jadad	
Mean (SD)	2.6 (1.2)
Median (range)	2 (0 – 5)
Allocation Concealment	
Adequate	65 (21.7)
Unclear	227 (75.7)
Inadequate	8 (2.7)
Risk of Bias	
Low	23 (7.7)
Unclear	99 (33.0)
High	178 (59.3)
CONSORT Statement	
Items fully addressed (median, range)	15 (4-22)
Items partially addressed (median, range)	5 (0-14)
Items not addressed (median, range)	2 (0-7)
Trial registered	
Declared in publication	37 (12.3)
Registration found online	69 (23.0)
Study protocol available from corresponding author	2/290 (0.7)

Table 2.3. 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%)

Table 2.4. Trial characteristics and quality assessment stratified by trial registration and overall risk of bias (N=300)

Trial Characteristics	N	Trial Registered		Risk of Bias		
	300	**Yes (N=69;23%)**	**No (N=231;77%)**	**Low (N=23;8%)**	**Unclear (N=99;33%)**	**High (N=178;59%)**
Impact factor (median, range)	294	4.017 (0.581-52.589)	1.883 (0.080-15.484)	2.948 (0.475-10.169)	1.850 (0.329-52.589)	2.342 (0.080-28.638)
Continent of corresponding author						
Africa	11	4 (5.8)	7 (3.0)	1 (4.4)	4 (4.0)	6 (3.4)
Asia	58	6 (8.7)	52 (22.5)	6 (26.1)	27 (27.3)	25 (14.0)
Australia	16	1 (1.5)	15 (6.5)	2 (8.7)	7 (7.1)	7 (3.9)
Europe (excluding UK)	91	17 (24.6)	74 (32.0)	6 (26.1)	27 (27.3)	58 (32.6)
North America	87	30 (43.5)	57 (24.7)	5 (21.7)	19 (19.2)	63 (35.4)
South America	7	2 (2.9)	5 (2.2)	-	2 (2.0)	5 (2.8)
United Kingdom	30	9 (13.0)	21 (9.1)	3 (13.0)	13 (13.1)	14 (7.9)
Funding source specified	194	62 (89.9)	132 (57.1)	23 (100.0)	49 (49.5)	122 (68.5)
Industry supported	67	24/62 (38.7)	43/132 (32.6)	7/23 (30.4)	8/49 (16.3)	52/122 (42.6)
Primary outcome explicitly stated	123	41 (59.4)	82 (35.5)	14 (60.9)	34 (34.3)	75 (42.1)
Statistically significant outcome	230	47 (68.1)	183 (79.2)	15 (65.2)	83 (83.8)	132 (74.2)
Data Monitoring Committee	14	9 (13.0)	5 (2.2)	1 (4.4)	5 (5.1)	8 (4.5)
Jadad score (mean; median, range)	300	2.99 (3; 0-5)	2.44 (2; 0-5)	3.96 (4; 3-5)	2.24 (2; 1-5)	2.56 (2; 0-5)
Allocation Concealment						
Adequate	65	24 (34.8)	41 (17.8)	20 (87.0)	15 (15.2)	30 (16.9)
Unclear	227	45 (65.2)	182 (78.8)	3 (13.0)	84 (84.9)	140 (78.7)
Inadequate	8	-	8 (3.5)	-	-	8 (4.5)
Trial registered	69	NA	NA	11 (47.8)	10 (10.1)	48 (27.0)
Risk of Bias						
Low	23	11 (15.9)	12 (5.2)	NA	NA	NA
Unclear	99	10 (14.5)	89 (38.5)			
High	178	48 (69.6)	130 (56.3)			

Table 2.5. Author responses to follow-up survey (N=145)

Survey Question	N (%)
Was your trial registered with a public trial registry?	
Yes	61 (42.4)
No	83 (57.6)
No response	1
What were your reasons for registering your trial (select all that apply)?	
I believe that trials should be registered as a means of full public disclosure	30 (68.2)
I endorse the statement regarding public trial registration made by the ICMJE	23 (52.3)
Trial registration is necessary for publication in some peer-reviewed journals	32 (72.7)
Trial registration was required by the funding agency	5 (11.4)
Trial registration was required by the Research Ethics Board	9 (20.5)
Trial registration is institutional policy	2 (4.5)
Other	3 (6.8)
No response	101
What were your reasons for not registering your trial (select all that apply)?	
Lack of time	3 (4.5)
Lack of resources	5 (7.6)
I was not familiar with the process for trial registration	39 (59.1)
Cost associated with registration	4 (6.1)
I don't see a benefit to trial registration	1 (1.5)
Trial was initiated prior to registration endorsement by the ICMJE	34 (51.5)
No formal requirement	4 (6.1)
Other	7 (10.6)
No response	79

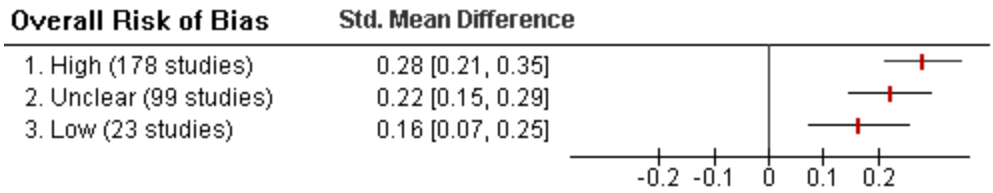

Figure 2.1. Effect size estimates according to overall risk of bias.

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Chapter 3

Do health care institutions value research? A mixed methods study of barriers and facilitators to methodological rigor in pediatric randomized trials[2]

Michele P Hamm, Shannon D Scott, Terry P Klassen, David Moher, Lisa Hartling

3.1. Background

"We as an institution, as a profession, don't actually sell research as being an important thing that we do in hospitals. And it should be."

There is a growing body of literature documenting the methodological limitations of published randomized controlled trials (RCTs) in pediatrics.[1-7] Of particular concern is the evidence that RCTs in child health are susceptible to a high risk of bias, increasing the likelihood that reported treatment benefits and/or harms are being exaggerated.[8-10] In order to ensure clinical relevance and to prevent unnecessary and wasteful research, it is crucial that measures are taken to maximize the internal validity of studies that are conducted.[11,12] The global investment in research is enormous, with funding of $100 billion annually,[11] plus the time and effort committed by the researchers, clinicians, and children and families. When participants agree to take part in a trial, they expect that the study will be conducted and reported to the highest standard to accurately answer the research question. When this expectation is met, trial results are important in providing children with the best possible treatment; however, when biased research is conducted instead, research dollars and professionals' time are wasted, and the children's contributions are unavailing.

Evidence describing the negative impact of bias on RCTs and how to minimize it is available,[13-22] as is research on a number of specific challenges inherent in

[2] *A version of this chapter has been published. Hamm et al. BMC Medical Research Methodology 2012; 12:158. The BioMed Central copyright and license agreement is available in Appendix B.*

conducting RCTs in pediatrics,[23-27] such as recruitment and consent procedures. However, the research-practice gap regarding methodological rigor in this population has not yet been addressed.

As the first step in the development of a knowledge translation strategy to address the reduction of bias in pediatric RCTs, the objective of this study was to determine and describe the barriers and facilitators that pediatric trialists face in the design and conduct of unbiased trials, with an emphasis on the Canadian context. Quantitative survey and qualitative interview data were collected to gain a broad perspective of the problem and researchers' experiences.

3.2. Methods

3.2.1. Design

We used an explanatory mixed methods design, with semi-structured interviews building upon the results of a quantitative survey. We connected data from the two phases to provide detailed descriptions of the barriers and facilitators pediatric trialists face in designing and conducting studies with high internal validity.[28] We obtained ethical approval from the Health Research Ethics Board at the University of Alberta.

3.2.2. Data collection

Quantitative: survey

We sent an Internet-based survey (SurveyMonkey) to a sample of Canadian and international pediatric trialists between September 2010 and February 2011. We searched the Cochrane Central Register of Controlled Trials for pediatric RCTs published in 2008 and 2009 and identified 7,535 articles (Appendix H). Corresponding authors of all relevant trials identified using a Canadian-specific search filter (n=90), and a geographically representative sample of 600 international trialists chosen from a randomly ordered list were invited to participate in the survey. We sent an invitation e-mail with a link to the survey and two reminder e-mails separated by two week intervals (Appendix I). The

questionnaire was informed by The Cochrane Collaboration's Risk of Bias tool,[29] the BARRIERS Scale,[30] and the framework proposed by Cabana et al.,[31] described in Box 3.4 (Appendix J).

Twelve methodologists and clinicians evaluated the questionnaire for appropriateness and accuracy of content and 5 national and international pediatric trialists completed pilot testing for clarity and ease of use; we made revisions based on their feedback. The survey included 23 questions and pilot testing indicated that it would take approximately 15 minutes to complete. We developed items to determine: 1) researcher knowledge and awareness of bias; and 2) perceived barriers and facilitators in conducting clinical trials.

Due to a low response rate using the sample described above (154/644; 23.9%), we expanded the survey population to recruit participants from the membership of the Maternal Infant Child and Youth Research Network (MICYRN), a Canadian network linking investigators from 17 academic health centres involved in pediatric clinical research. We identified potential respondents through a publicly available network inventory maintained by MICYRN (http://www.micyrn.ca/Networks.html) and invited all individuals listed as network contacts via email to participate in both the survey and the interview portion of the study (n=163). The survey included an item asking whether respondents would be willing to be contacted for an interview, and if so, to provide their name and preferred means of initial contact. As a result of problems with access to SurveyMonkey, we administered this wave via REDCap, an alternate secure, online application for managing surveys.

Qualitative: interviews

Due to low participation rates from survey respondents, we augmented recruitment with members of MICYRN with trial experience and referrals from participants and established pediatric trialists. We used purposive sampling based upon pediatric subspecialty and geographic location, aiming to reach saturation,

which typically occurs around 12 participants.[32] Interviews followed a semi-structured format built upon the results of the survey and were focused on participants' experiences and attitudes towards conducting pediatric research and how these interacted with the appropriate design and conduct of methodologically sound trials (Appendix K). Each participant was sent an electronic consent form that they signed and returned via fax or email prior to the conduct of the interview (Appendix I). Interviews were 30 to 60 minutes and conducted by telephone by the lead author between April and July 2011. All interviews were recorded and transcribed verbatim.

3.2.3. Data analysis

We analyzed survey data descriptively, using means and standard deviations, medians and interquartile ranges (IQR), or proportions where appropriate. We used a qualitative descriptive approach,[33] using content analysis to code interviews, identifying categories in the data and patterns in beliefs and values that could help explain the potential for bias in pediatric RCTs.[34] Coding was conducted by the lead author in consultation with the rest of the study team (Appendix L). We conducted qualitative data collection and analysis concurrently, following an iterative process. We integrated the survey and interview data at the data interpretation phase,[35] using the method of connecting data.[28] We used Stata and NVivo to manage quantitative and qualitative data, respectively.

3.3. Results

The survey response rate was 23.0% (186/807) and 13 interviews were conducted. Characteristics of the survey and interview participants are described in Tables 3.1 and 3.2. Survey results were similar across geographic boundaries and were therefore combined and used as a whole to inform a detailed examination of how barriers and facilitators manifest in Canadian research. Results are presented according to their classification as individual, institutional, or policy level factors. Themes are outlined in Table 3.3.

3.3.1. Individual factors

Survey findings indicated that 68.1% of respondents agree that bias is a problem in pediatric RCTs and 72.0% reported that they felt there was sufficient evidence to support the need to change some aspects of how RCTs are conducted. However, knowledge of bias among respondents was variable. There was no consistency in responses to questions which asked the respondent to rate the degree to which they agreed that a study design factor would introduce bias into a study. Identification of specific biases was strongest for sequence generation, blinding, and selective outcome reporting, while there was more uncertainty surrounding identification of problems with allocation concealment, incomplete outcome data, and "other sources of bias" (Appendix J). Despite this range of awareness of issues relevant to bias, 94.2% of respondents felt confident in their ability to evaluate the quality of published trials.

The interviews highlighted two important themes regarding barriers and facilitators at the individual level: knowledge and training regarding research methods, and engagement or ownership in the research process (Box 3.1). While most survey respondents indicated that bias is a problem, the interview data suggested that trialists often do not have the knowledge to first, recognize, and second, address bias in their studies. They often mentioned a lack of formal training, instead relying on skills learned on the job.

Conversely, a sense of ownership can contribute to a rigorous study design. Actively taking responsibility for the direction of the trial was seen as an opportunity for the investigators to generate enthusiasm, gain support, and educate colleagues about the rationale for rigorous methodology and how it impacts the ability to accurately answer the research question.

> "Listen to what [your colleagues] need to execute the study so that when you develop your protocol, you've built that into the approach. Or, if you

couldn't, you've at least had that dialogue with them about how scientifically you can't be as flexible as might be ideal… so that they at least understand the rationale."

3.3.2. Institutional factors

While 93.0% of survey respondents demonstrated an interest in learning about and staying current with literature describing and analyzing research methods, only 50.3% felt that they were able to do so due to other constraints. Logistical issues such as meeting institutional requirements (29.2%) and having sufficient staff (30.4%) were identified as challenges, while access to knowledgeable colleagues (92.8%) was identified as the most significant facilitator (Appendix J).

Consistently, interview respondents felt that environmental factors within their institutions were not conducive to research, often as the result of perceptions of research (Box 3.2). They reported the underlying culture to be overwhelmingly negative towards research at all levels, with resistance from trainees, nurses, physicians, administrators, and the pharmaceutical industry. While respondents felt that the products of research tend to be valued once they are demonstrated to improve practice, they stated that there is little appreciation of the methods necessary to achieve that goal. Logistically, respondents felt that having staff dedicated to research would improve this situation, as research procedures would then not consistently be placed at the lowest priority. Recognition of the division between the paradigms of clinical care (e.g., protecting the interests and comfort of patients) and clinical research (e.g., maintaining clinical equipoise) was also identified as a challenge. Clinical investigators often have difficulty with this distinction, which allows for the possibility of compromised trial protocols.

"I think a lot of investigators really have a hard time separating what decision they would make clinically from what decision they would make as part of a trial… because the feeling is I want to be convenient to the family, and I really know this stuff because I'm an expert in this clinical

> area, and I don't think they realize that there's a pretty clear demarcation between what you do in clinical care and what you do as research."

The degree to which institutional barriers were perceived as a threat to research varied according to the size of the site of the respondent. A clear distinction was noted between larger research-intensive institutions and other sites in which researchers struggled due to a lack of infrastructure. Trialists from the former viewed the conduct of research much more positively and generally felt that they had the necessary resources available to conduct rigorous trials, while those from the latter reported greater levels of difficulty positioning their research as an important part of the clinical landscape.

> "Space, resources, and training for research assistants, research managers, graduate students… there's all sorts of hurdles and headaches around those things that I think most established clinical research programs… already know how to make the system work."

Similar to the survey results, cohesive study teams with positive working relationships were reported as the most significant facilitator to conducting rigorous trials. At the institutional level, this often included combining the expertise of experienced trialists, methodologists, and the staff that would be responsible for implementing the trial; however, this integration was more common at sites with more support for research. Positive relationships were also mentioned in the context of subspecialties, with productive research networks across sites enabling researchers to benefit from a collective expertise, as well as facilitating study-specific elements such as the conduct of multi-centre trials. A final facilitator, which was more prominent in certain institutions than others, was a reliable internal review process. Respondents viewed this as a major asset when it was available, but many felt that existing processes were fragmented and inconsistent.

3.3.3. Policy factors

All interview respondents felt a lack of incentive to conduct pediatric trials. Difficulty in securing funding was frequently mentioned, but beyond that, participants reported that it is challenging to justify including financial support for a methodologist in grant application budgets in an environment where the funds awarded are anticipated to be less than requested. In this context, there is less assurance that study teams can include the necessary expertise. Meeting the requirements of several research ethics boards also presents a challenge, particularly with the preponderance of multi-centre trials in pediatrics. With separate ethics approval processes at each institution, the process can be lengthy and protocols are oftentimes changed to meet the inconsistent requests of the individual review panels (Box 3.3).

3.3.4. Specific biases and pediatric-specific challenges

Addressing specific biases, survey and interview respondents reported challenges with blinding most frequently, which included the cost of providing a placebo, difficulties in blinding non-pharmacological interventions, and blinding all relevant parties, including parents. Other issues that were mentioned included difficulty getting adequate follow up in settings without an established clinician-patient relationship, parental resistance to randomization, and group imbalances due to small sample size.

3.4. Discussion

Bias is a recognized concern among pediatric trialists; however they may be lacking the knowledge, willingness, or resources to properly address it. Internal validity did not emerge as a primary concern in the analyses, being overshadowed by issues related to the pragmatics of running a trial and the generalizability of the results. While these issues warrant a great deal of consideration, it is crucial that studies start out being methodologically rigorous as this is a prerequisite for generalizability.

The major barriers to minimizing risk of bias in trials were related to awareness and environment. With little emphasis on research methodology in clinical curricula, many investigators are not adequately prepared to design trials with high levels of internal validity or to recognize and attend to issues as they arise. The existing *ad hoc* training system very likely contributes to an emphasis on certain areas and a deficit in others, as demonstrated by the disproportionate focus by respondents on issues related to external validity (i.e., generalizability of study results), despite being questioned on issues relevant to internal validity (i.e., avoiding bias through methodologically rigorous design). Additionally, the predominantly negative attitudes surrounding the research process reinforce the acceptance of sub-optimal RCTs. While research findings may be valued, more effort is required to ensure that the importance of high quality research is recognized at all stages, and by all stakeholders. Pediatric oncology is often cited as a model in developing an environment that fosters research. Available infrastructure and consistency in study protocols has resulted in the successful integration of research and clinical care leading to marked improvements in survival and other outcomes.[24,36-37] By embracing research as a critical component of providing best care, rather than viewing it as an imposition, investigators and clinicians in oncology have shown that setting a standard for conducting rigorous trials is an achievable goal with tangible benefits and impressive health outcomes.

Positive relationships that support the development of an interest in research are particularly relevant in an environment in which most training is dependent on mentorship and reinforcement from experienced trialists. Within this context, clinician-scientists have a key role in bridging the gap between the worlds of research and clinical practice. Combining knowledge of proper methodology with an appreciation for the demands of the clinical setting will increase the likelihood of producing both valid and realistic trials. Research networks such as the Canadian Critical Care Trials Group (CCCTG) and Pediatric Emergency Research Canada (PERC) have been quite successful in using this strategy, facilitating high quality trials by promoting a positive culture of research,

providing access to individuals with expertise, and offering support and collegiality.[38,39]

With a solid evidence base demonstrating the gaps in methodological quality in pediatric RCTs,[1-10] the research agenda must now focus on knowledge translation. Using barriers and facilitators identified by the target end-users, it will be important to develop tailored strategies to overcome the gap between what is known about methodological processes and how trials are designed and conducted in practice. This is one of the stated aims of StaR Child Health, an international initiative dedicated to improving the quality of pediatric clinical research.[40]

3.5. Strengths and limitations

An advantage of this study is that it combines the breadth of survey responses with the depth of interview responses, allowing for a detailed picture of the barriers and facilitators pediatric trialists face in the conduct of methodologically rigorous trials. While the response rate to the survey was low, bringing into question the representativeness of the sample, it was in line with evidence that both electronic surveys[41] and physician surveys[42] are associated with low responses. However, respondents represented a wide range of pediatric specialties, training backgrounds, and geographies, helping to give shape to the subsequent interviews. While they may have represented researchers with a higher level of interest in methodology, the survey responses were used to form the interviews, in which researchers with trial experience were of interest so as to be able to account for the barriers and facilitators in pediatric research with first-hand knowledge. The recruitment of additional survey participants from the membership of MICYRN slightly changed the balance of geographical representation; however the Canadian context was weighted heavily throughout the study, therefore our emphasis was unchanged. The response rate to requests for interview participation was also low, but with our expanded recruitment strategy we were able to achieve saturation. The interviews emphasized the Canadian context and therefore can be used to inform future developments within

the national health care and research framework, as well as provide considerations relevant to other settings.

3.6. Conclusion

Clinical research is inherently challenging, but these results can be used to focus efforts on improving the validity of trials that are conducted. The evidence is clear that improvement is necessary in pediatric RCTs and a substantial body of knowledge has accumulated around how to minimize bias. Before the conduct of trials can improve, though, awareness of bias and attitudes towards research must be addressed through a shift in culture. Research must be reframed as a valuable component of health care education, practice, and decision-making.

3.7. Acknowledgements

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Table 3.1. Demographics of survey population

Variable	n (%)
Total returned surveys	186/807 (23.0)
Undeliverable surveys	46/853 (5.4)
Professional time spent on research-related activities	
0%–25%	34 (18.3)
26%–50%	28 (15.1)
51%–75%	48 (25.8)
76%–100%	38 (20.4)
No response	38 (20.4)
Involvement in RCTs – median number of trials (IQR)	
As a principal investigator	3 (1-5)
As a member of the study team	5 (2-10)
Discipline trained in*	
Medicine	83 (44.6)
Research	69 (37.1)
Psychology	17 (9.1)
Allied healthcare	13 (7.0)
Nursing	11 (5.9)
Other	9 (4.8)
No response	38 (20.4)
Pediatric subspecialty	
Public health	16 (8.6)
Developmental, psychosocial, and learning problems	14 (7.5)
Mental health or psychiatry	13 (7.0)
Neonatology	11 (5.9)
Endocrinology and nutrition	10 (5.4)
Emergency medicine or critical care	9 (4.8)
Infectious diseases	9 (4.8)
Hematology or oncology	7 (3.8)
Oral health	6 (3.2)
Allergy and immunology	5 (2.7)
Anesthesia	5 (2.7)
General pediatrics or family medicine	5 (2.7)
Other	47 (25.2)
No response	29 (15.6)
Geographic region of corresponding author	
Asia	10 (5.4)
Australia and New Zealand	12 (6.5)
Canada	47 (25.2)
Europe	25 (13.4)
South America	3 (1.6)
USA	46 (24.7)
No response	43 (23.1)
Setting of employment*	

University or academic centre	124 (66.7)
Hospital	48 (25.8)
Solo practice	4 (2.2)
Group practice	4 (2.2)
Industry	4 (2.2)
Other	7 (3.8)
No response	39 (21.0)

*More than one selection possible.

Further details on collapsed categories are available from the authors.

Table 3.2. Characteristics of interview participants

Variable	n (%)
Total interviews	13 (100)
Source of recruitment	
Survey	3 (23.1)
MICYRN	3 (23.1)
Referral from participants/established trialists	7 (53.8)
Discipline(s) trained in	
Medicine	7 (53.8)
Research	2 (15.4)
Medicine and Research	4 (30.8)
Pediatric subspecialty	
Anesthesiology	1 (7.7)
Clinical epidemiology	1 (7.7)
Critical care	2 (15.4)
Emergency medicine	3 (23.1)
Infectious disease	1 (7.7)
Neonatology	1 (7.7)
Neurology	1 (7.7)
Oncology	1 (7.7)
Psychology	1 (7.7)
Rheumatology	1 (7.7)
Geographic region of participant	
Alberta	2 (15.4)
British Columbia	2 (15.4)
Ontario	6 (46.2)
Quebec	1 (7.7)
USA	2 (15.4)

Table 3.3. Interview themes and relevance to risk of bias

Category	Theme	Relevance to Risk of Bias
Barriers		
Individual	Knowledge	- Little formal training in research methods, therefore bias is likely due to a lack of knowledge of how it is introduced.
Institutional	Clinical care vs. clinical research	- Decisions made clinically rather than per the trial design can lead to protocol deviations, e.g. interference with randomization sequence.
	Culture	- Research is often viewed negatively in the clinical setting, leading to little value placed on following the trial protocol when it deviates from usual care.
	Logistics	- Demands on time and space can put research at a low priority and tasks may not be done according to protocol, e.g. ensuring safeguards are in place to maintain blinding.
Policy	Administration	- Budget constraints can limit hiring external methodological expertise if necessary; ethics requirements for methodology are inconsistent, leaving protocols subject to change.
	Pediatric-specific challenges	- Blinding parents; investigators are less willing to inconvenience families with strict protocols; fewer trials has meant less competition for developing the best methodology.
Facilitators		
Individual	Ownership	- The trial will be more successful when the investigators take responsibility for generating support and ensuring rigor.
Institutional	Acceptance	- Researcher understanding of the clinical setting facilitates the acceptance of research methods by the practitioners.
	Cohesive study team	- Consulting experienced trialists and methodologists contributes to a more rigorous and well thought out study, in terms of both validity and feasibility.
	Infrastructure	- Protected research time and dedicated research staff facilitate trial design and conduct.
	Verification	- Checks on the science facilitate high quality, e.g., reliable review processes and guidance from trusted third parties.

Box 3.1. Perspectives on individual-level factors

Barriers:

02: Probably we don't look at, we don't know all the bias that can be, that can happen in a trial because we don't check, we don't believe there's bias. We may miss some, we may forget some, and then do not report the bias because we don't know it exists.

06: I've kind of learned on the job, which is why I'm not fully confident that I have all the skills.

07: Because there's almost zero research training in the clinical curriculum for most clinicians these days. Like there's almost nothing in the med school program, there's almost nothing in the rehab program – there really needs to be somebody on the protocol who's got a little bit more training.

10: Well you know it's often when people go to write up a protocol, either they're not totally aware of how this whole bias thing works and to them, you know the fact that you randomize people by the day of the week they present, that sounds good enough.

Facilitators:

04: So you really have to take the time to engage people and be the one that's proactive, engaging them. Because they're busy, they might not even know what your study is unless you're the change agent that really goes out there and talks to them about it and gets them motivated about why you think it's important.

Box 3.2. Perspectives on institution-level factors

Barriers:

09: I think that other people view [research] as kind of a thorn in their side. It's something they play along with if they have to and the division head tells them they have to.

09: You work separately or in parallel and not necessarily the team as much, and I think that's part of the challenge. You view the study as important, they view the results as important, but they don't want to go through the pain of finding out the results because it impacts on what they do clinically.

03: Where we get into the biggest problems is if we take a person who's very knowledgeable and very confident in how to care for patients with [*disease*], so they're experts and masters in clinical care, and they just assume that that carries over into being an expert in clinical research.

Facilitators:

01: So because we get donated funds, a fairly large amount of donated funds proportionally speaking in [*disease*], we're able to support the personnel to perform the trials.

06: We have the help of the research institute and you can have a person for any kind of question or any kind of design that can help, and we have access to those kinds of resources.

09: I think the fact that [*research network*] is there enables you to think of multi-centre RCTs, whereas if it wasn't there, you'd kind of have to go and find things from scratch. But by existing, it brings people together with shared interests and I think that that is a huge asset when it comes to even the thought of designing a multi-centre RCT. It's like you want to design one for [*research network*].

07: [*Research institute*] has a great model where they require any grant that's going out for external funding to be reviewed by three people from inside the institution.

Box 3.3. Perspectives on policy-level factors

Barriers:

13: We all tend to want to make the budget as small as we can to increase our chances to actually get it funded and the reality is that some trials really require the full-time effort of somebody who's got a lot of experience, and therefore comes with a price tag. And it can be hard to make the argument to ensure that you've got funding, right? So I think that's where you start cutting other corners, and you don't have the data quality, and at the end of the day, you maybe don't have the rigorous, homerun kind of trial that you had envisioned.

02: *(regarding ethics review at multiple sites)* Most of the problem is to ask for revisions and they are not consistent one between the others. So you can have a question in one and the other one… wants a different answer.

Box 3.4. Tools used for survey development

Risk of Bias tool: Used to assess the internal validity of RCTs. It is comprised of seven domains supported by empirical evidence: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and "other" sources of bias.[29]

BARRIERS Scale: Widely used to identify general barriers to research utilization, particularly in nursing. Barriers are categorized into factors related to the individual, setting, research, and presentation.[30,43]

Cabana framework: Developed by Cabana et al.[31] as part of an evaluation of barriers to physicians' adoption of clinical practice guidelines. This framework includes 10 major factors, grouped into categories related to knowledge, attitudes, and behaviour.

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Chapter 4

Use of social media by health care professionals and trainees: a scoping review[3]

Michele P Hamm, Annabritt Chisholm, Jocelyn Shulhan, Andrea Milne, Shannon D Scott, Terry P Klassen, Lisa Hartling

4.1. Background

Advances in technology have markedly changed the way health care providers and consumers access and use information. Social media tools such as Facebook, Twitter, and YouTube have been used for such purposes as to train medical personnel, to provide information to patients, and to allow rapid communication in times of crisis.[1] Currently, Facebook has 955 million active users, with approximately 50% of those accessing the site in any given day;[2] as of February 2012, 15% of adults using the Internet in the United States were on Twitter, up from 8% in November 2010;[3] and YouTube has more than 800 million unique users monthly, with over 72 hours of video uploaded every minute.[4]

Social media encompasses a group of online applications that allow for the creation and exchange of content generated by users.[5] It represents a significant evolution in the way in which information can be developed and shared, including between people who may not have been able to connect without this technology. The past decade has seen a widespread shift from knowledge primarily created and disseminated by individuals to an environment in which all users with Internet access have the opportunity to play a participatory role in a more collaborative information sharing system.[5,6]

Social media tools can be categorized into five groups, as outlined in Table 4.1: 1) collaborative projects (e.g., Wikipedia); 2) blogs or microblogs (e.g., Blogger,

[3] *A version of this chapter has been submitted for publication. Hamm et al. Academic Medicine.*

Twitter); 3) content communities (e.g., YouTube); 4) social networking sites (e.g., Facebook); and 5) virtual gaming or social worlds (e.g., Second Life).[5] Adoption of these tools has been slow in health care;[7] however the uptake of social media has been widely advocated[7-14] and has potential for use in knowledge translation. Knowledge translation, or implementation science, seeks to close the gaps between knowledge and practice[15] and therefore focuses on novel forms of dissemination. Proponents of the use of social media in health care point to three key features that make these tools highly effective, which also overlap with the objectives of knowledge translation: personalization, presentation, and participation.[16] The tailoring of content allows users to access and share information that is most valuable to them, while the versatility of social media as a whole creates numerous options for the presentation of information. It is immediate, allowing for the timely dissemination of relevant information, and there are multiple formats that can be used (e.g., microblogs, social networking sites), depending on the purpose of the tool and the preferences of the target population. The collaborative nature of social media allows for a meaningful contribution from all user groups. In *The Wisdom of Crowds*, James Surowiecki stated that, "Groups are remarkably intelligent, and are often smarter than the smartest people in them."[17] This sentiment has been echoed by supporters of social media, who promote the benefits of this synergistic relationship.[18]

The use of social media in health care has also been criticized. One of the primary concerns centers around patient privacy and confidentiality.[8] With such a wide and instantaneous reach, an error in judgment involving an online post can have profound implications in terms of trust and professionalism.[19,20] The availability of misinformation is also a risk as health care providers cannot control what is posted or discussed.[7,21] Inappropriate substitution of online information or advice for in-person visits to a health care provider, with potentially harmful results, has also been cited as a limitation of the use of social media and the Internet in general.[7,22]

Despite enthusiasm surrounding the potential use of social media, there is little evidence describing the current state of the science and whether or not these tools can be used to benefit education and practice in health care. Given the rapid expansion of this technology into health care, it is important to evaluate the new opportunities that have become available.

The objectives of this study were to map the existing literature examining the use of social media in health care professional and trainee populations, to determine the extent and type of evidence available in order to inform more focused knowledge syntheses, and to identify gaps for future research. The specific questions guiding this scoping review were: 1) What social media tools are being used in health care professional and trainee populations? 2) In which disciplines and specialties are social media tools being used? 3) For what purposes are social media tools being used in health care professional and trainee populations? 4) What types of evidence and research designs have been used to examine social media tools?

4.2. Methods

This scoping review on the use of social media in professional populations was conducted in parallel with a review on the use of social media in patient and caregiver populations; therefore the literature search and screening for study eligibility were conducted concurrently. The review followed a protocol that we developed *a priori*.

4.2.1. Search strategy

A research librarian searched 11 databases: Medline, CENTRAL, ERIC, PubMed, CINAHL Plus Full Text, Academic Search Complete, Alt Health Watch, Health Source, Communication and Mass Media Complete, Web of Knowledge, and ProQuest. Dates were restricted to 2000 or later, corresponding to the advent of Web 2.0; no language or study design restrictions were applied. The search strategy is provided in Appendix M.

4.2.2. Study selection

Two reviewers independently screened titles and abstracts of studies for eligibility. The full text of studies that were assessed as "relevant" or "unclear" were then assessed independently by two reviewers using a standard form (Appendix N). Discrepancies were resolved by consensus or adjudication by a third party.

Studies were included if they reported primary research (quantitative or qualitative), were conducted in a population of health care professionals or trainees, and examined the use of a social media tool (Appendix N). Social media was defined according to Kaplan and Haenlein's classification scheme,[5] which includes the following categories: collaborative projects, blogs or microblogs, content communities, social networking sites, and virtual worlds. We excluded studies that examined mobile health (e.g., apps), one-way transmission of content (e.g., podcasts), and real-time exchanges mediated by technology (e.g., Skype, chat rooms). Electronic discussion forums and bulletin boards were included as they incorporate user-generated content and were judged to lie within the spectrum of social media. Outcomes were not defined *a priori* as they were to be included as part of our description of the field. Likely categories for objectives and outcomes were adapted for professionals and trainees from those outlined in Coulter and Ellins' proposed framework for strategies to inform, educate, and involve patients.[23,24]

4.2.3. Data extraction

Data were extracted using standardized forms and entered into Microsoft Excel (Microsoft, Redmond, WA) by one reviewer and a 10% sample was checked for accuracy and completeness by another.[25] Reviewers resolved discrepancies through consensus. Extracted data included study and population characteristics, description of the social media tools used, objective of the tools, outcomes measured, and authors' conclusions (Appendix O).[26]

4.2.4. Data synthesis

Data were synthesized descriptively in order to map different aspects of the literature as outlined in our key questions. Studies were grouped according to tool and audience. As discussion forums may be considered precursors to modern social media platforms, findings are presented both for all included studies and for studies that investigated tools other than discussion forums. Descriptive statistics were calculated using StataIC 11 (StataCorp, College Station, TX).

4.3. Results

Ninety six studies were included in the review. Figure 4.1 outlines the flow of studies through the inclusion process and Table 4.2 provides a description of included studies. The majority were conducted in North America (62.5%) and Europe (21.9%), most commonly in the United States (56.3%) and the United Kingdom (9.4%). We extracted data on the countries involved in each study, and it rarely differed from the country of the corresponding author. The exception was for studies examining pre-existing, well-established tools such as Wikipedia, where the audience was not restricted by geography. The median duration of included studies was four months, ranging from one month to four years. For the total sample, the median start date was 2006 (range 1995 to 2011). When discussion forums were removed, study dates were more recent (median 2008, range 2000 to 2011). The majority of authors (64.6%) concluded that there was evidence to support the use of social media in educational or practice settings.

4.3.1. Social media tools used

Table 4.3 outlines the social media tools that were studied. Discussion forums were the most commonly studied tools, included in 44.8% of the studies. In 32.3% of the studies, the social media tool was included as a component of a complex intervention. For specific categories of tools, blogs and microblogs were the most commonly studied (28.1%), followed by collaborative projects (20.8%),

social networking sites (16.7%), content communities (13.5%), and virtual worlds (9.4%).

Often investigators created their own tool to evaluate, but in studies that made use of a pre-existing tool and in those examining usage patterns and preferences, the most common tools were Facebook, YouTube, Twitter, Wikipedia, and Second Life (Figure 4.2).

4.3.2. Social media user groups

Three major categories could be used to group social media users: education, practice, and general purpose (Table 4.4). Education comprised the largest group, encompassing 68.8% of the studies. When broken down by discipline, the highest representation was in medical education (22.9%), followed by nursing education (17.7%). Social media was used to a limited extent in continuing education or professional development, however nearly all interventions were aimed at students or residents. In all disciplines, a range of social media tools was used. In allied health, interdisciplinary education, medicine, and nursing, discussion forums were the most commonly used; however, blogs or microblogs were used most often in dentistry/dental hygiene and in public health, and collaborative projects were included in all three pharmacy studies.

Use of social media in professional practice was examined in 18.8% of studies (Table 4.4). Medicine was again the most common discipline. As with education, a range of tools was used, with the exception of virtual worlds. Blogs or microblogs were used most frequently, often in the context of general posts targeted for other professionals.

The general purpose category of social media users describes studies in which health care professionals were asked about their perceptions and attitudes towards these technologies, or studies that analyzed health-related content posted online, either descriptively or for accuracy. This category made up 10.4% of the study

sample (Table 4.4). Of these ten studies, four were cross-sectional examinations of how social media is being used, and six were content analyses of user-generated general health or medical online posts.

Specialties that appeared more than once are listed in Table 4.4. Administration, critical appraisal, and research were grouped together and appeared most frequently (11.5%), followed by public health (9.4%). In a number of studies, the investigation ranged across multiple specialties (34.4%). The choice of tool used did not seem to vary by specialty.

4.3.3. Purposes of social media use

The objectives of the social media tools were broken down into three categories: knowledge, skills, and communication (Table 4.3). In 61.5% of evaluations, the purpose of the tool was to facilitate communication. This ranged from peer-to-peer or instructor-to-student communication within classes, to communication between clinicians and their patients, to clinicians communicating with the public via tools such as blogs. Nearly all blogs or microblogs (92.6%) and social networking sites (93.8%) included communication as a main focus. Communication was least prominent in tools that were part of a complex intervention (45.2%). Knowledge was addressed in 42.7% of studies and skills in 20.8%. Collaborative projects (55.0%) and discussion forums (51.2%) were often intended to increase knowledge; virtual worlds had the highest representation for use in improving or learning clinical skills (44.4%).

Three categories were used to classify the outcomes measured in each of the included studies: clinicians' knowledge, clinicians' experience, and professional behaviour (Table 4.5). Most studies included outcomes related to experience, which included satisfaction and measures of communication. The least common measures were related to professional behaviour, and when reported, were mostly related to skills. Professional boundaries were also included in this category, encompassing topics such as how personal and professional lines could be blurred

with easily accessible information online and the use of social media by professionals to access information on their patients. When discussion forums were excluded from the analysis, there was less of an emphasis on measures that were prominent in educational settings, namely peer-to-peer and instructor-student communication. All of the studies that examined boundaries and privacy used tools other than discussion forums.

In most of the social media platforms, the most commonly measured outcome was related to peer-to-peer communication (Table 4.5). Only collaborative projects differed, measuring satisfaction most frequently.

4.3.4. Evaluation of social media use

Quantitative studies represented 56.3% of the sample, largely driven by the high proportion of cross-sectional studies (42.7%); qualitative studies comprised 21.9% of the sample (Table 4.2). Thirteen studies evaluated effectiveness: five randomized controlled trials, one non-randomized controlled trial, one controlled before-after study, and six before-after studies. Of the five randomized studies, four were in medical or dental education, and all five were evaluating discussion boards and targeting knowledge. Three studies found statistically significant improvements in knowledge gains and exam performance, one found a positive trend, and the other described the intervention as "promising." Similarly, six of the eight comparative studies using other designs were in educational settings (medicine, pharmacy, and dental hygiene). Greater diversity in tools was demonstrated, however, with evaluations of blogs, wikis, and virtual worlds. The intended purposes in this group were to improve both knowledge and skills. In 12 of the 13 studies, the authors' conclusions were positive with respect to the value of the social media intervention; however, only 6 reported statistically significant findings for their primary outcome.

The qualitative evaluations were largely conducted in nursing education (38.5%) and mainly focused on discussion forums (61.5%). Tools that facilitated

communication were examined in 76.9% of qualitative studies. Mixed methods studies made up 11.5% of the study sample and were used across disciplines. Surveys were included as one component of the design in 81.8% of these studies.

4.4. Discussion

The use of social media in health care education and practice is growing, and there is a significant body of literature examining its uses. To this point, most studies have been descriptive, either analyzing the content that exists online or investigating user preferences. Given the rapid evolution of the technology underlying social media, it is to be expected that early studies will be exploratory; however, the use of social media platforms and tools have become sufficiently widespread that studies of effectiveness would be beneficial, and would be particularly informative in the realm of education.

Due to the changing nature and continual progression of social media, establishing an operational definition to determine study eligibility proved challenging. Social media is defined inconsistently in the literature,[27,28] therefore Kaplan and Haenlein's classification scheme was selected on the basis of their use of discrete groups to categorize social media platforms, providing a framework, but allowing flexibility in the tools that could be included.[5] However, we still encountered grey areas, most significantly in deciding whether or not discussion forums should be included. While they did not fall under one of the pre-specified categories, it was felt that by encompassing user-generated online content, discussion and bulletin boards could be considered early versions of social media.

Despite the popularity of specific tools like Facebook and YouTube, most studies in this review evaluated tools that were developed specifically for the study team's purposes, most commonly blogs and wikis. This is logical, given that the populations studied were largely comprised of trainees, and these particular platforms lend themselves to educational settings because of the high level of detail they can incorporate. In cases where existing tools were examined, about

one third of studies asked participants about their current online presence. Studies specific to Facebook tended to be related to issues of professional boundaries and privacy. Those using YouTube and Second Life were skills-based, either demonstrating techniques or allowing practice.

While education was the predominant focus within this sample, social media use was demonstrated across disciplines, indicating widespread interest in its potential. With overlapping aims of facilitating instruction and an overarching focus on health care, findings from different professional groups are likely applicable across disciplinary lines and can be used to inform future applications and research in the area. Similarly, social media use was spread across a diverse range of specialties, with multidisciplinary coverage in approximately one third of studies. This suggests that while the content may be tailored to a particular group, the tools and platforms are relevant to diverse user groups.

Not surprisingly, communication was the most common purpose for using social media. Social media tools were created to enable interaction, and have expanded from primarily acting as channels of personal contact to also providing opportunities for professional conduct. Unique applications specific to the professional context have been explored, particularly with those tools that have been used to target knowledge and skills. With their intrinsic focus on personalization and interactivity, social media are ideally placed to become highly versatile tools that can be used to enable knowledge translation.

4.5. Limitations

Social media is a relatively new concept and is continually undergoing transformations. As such, there is no universal definition, adding complexity to the process of determining study eligibility. The constantly changing nature of social media also proved challenging in defining the literature search, and the novelty of the topic made it difficult to keep the search updated, with a steady influx of new reports. However, as this is a scoping review, the broad

categorization of the uses of social media was the focus and would not likely change with the addition of studies published since the search was conducted.

One third of the included studies examined social media as one component of a complex intervention, making it difficult to tease out the impact of the specific tool. This was largely a concern in studies that included discussion forums; other tools tended to be evaluated on their own.

4.6. Conclusions

This scoping review provides a map of the literature on the uses of social media for health care in professional and trainee populations. The existing body of evidence is extensive, focusing primarily on the use of social media in education and providing descriptive findings related to how it is being used. Considering the popularity and prevalence of these tools, it will be important for research to keep pace, delving further into whether or not social media is effective for professional and educational purposes through qualitative and quantitative research, and to focus on innovation to capitalize on the potential held by this technology.

Table 4.1. Categorization of social media tools

Tool	Description	Examples
Collaborative projects	Enable the joint and simultaneous creation of content by many end-users.	Wikis (e.g., Wikipedia) Social bookmarking applications (e.g., Mendeley)
Blogs or microblogs	Websites that display date-stamped entries. They are usually managed by one person but provide the opportunity to interact with others through the addition of comments.	Blogger Twitter (microblog)
Content communities	Allow for the sharing of media content between users, including text, photos, videos, and presentations.	BookCrossing Flickr YouTube Slideshare
Social networking sites	Enable users to connect by creating personal information profiles that can be accessed by friends and colleagues, and by sending emails and instant messages between each other.	Facebook MySpace LinkedIn
Virtual worlds	Platforms that replicate a 3D environment in which users can appear in the form of personalized avatars and interact with each other as they would in real life.	Second Life

Table 4.2. Description of included studies

Variable	Total – n (%)	Excluding discussion forums – n (%)
Total – N	***96***	***53***
Continent of corresponding author		
Asia	4 (4.2)	2 (3.8)
Australia	7 (7.3)	4 (7.5)
Europe	21 (21.9)	10 (18.9)
North America	60 (62.5)	35 (66.0)
South America	2 (2.1)	1 (1.9)
Not reported	2 (2.1)	1 (1.9)
Study start date – median (range)	2006 (1995-2011)	2008 (2000-2011)
Study duration – median (range)	4 months (1-48)	3 months (1-48)
Publication type		
Journal article	86 (89.6)	46 (86.8)
Abstract	7 (7.3)	6 (11.3)
Dissertation	3 (3.1)	1 (1.9)
Study design		
Quantitative		
Randomized controlled trial	5 (5.2)	1 (1.9)
Non-randomized controlled trial	1 (1.0)	1 (1.9)
Controlled before-after	1 (1.0)	1 (1.9)
Before-after	6 (6.3)	3 (5.7)
Cross-sectional	41 (42.7)	28 (52.8)
Qualitative		
Case study	5 (5.2)	1 (1.9)
Ethnography	1 (1.0)	-
Grounded theory	2 (2.1)	-
Phenomenology	2 (2.1)	-
Qualitative (other/not specified)	11 (11.5)	8 (15.1)
Mixed methods	11 (11.5)	5 (9.4)
Other		
Content analysis	10 (10.4)	5 (9.4)
Authors' conclusions		
Positive	62 (64.6)	30 (56.6)
Neutral	24 (25.0)	16 (30.2)
Negative	6 (6.3)	4 (7.6)
Indeterminate	4 (4.2)	3 (5.7)

Table 4.3. Description and objectives of social media tools used (N=96)

Tool	Total – n (%)	Objective – n (%)			
		Knowledge	Skills	Communication	Other
Total – n (%)		41 (42.7)	19 (20.8)	59 (61.5)	9 (9.4)
Collaborative project	20 (20.8)	11 (55.0)	3 (15.0)	11 (55.0)	3 (15.0)
Blog or microblog	27 (28.1)	5 (18.5)	4 (14.8)	25 (92.6)	3 (11.1)
Content community	13 (13.5)	4 (30.8)	3 (23.1)	10 (76.9)	-
Social networking site	16 (16.7)	4 (25.0)	1 (6.3)	15 (93.8)	-
Virtual world	9 (9.4)	4 (44.4)	4 (44.4)	5 (55.6)	2 (22.2)
Discussion forum	43 (44.8)	22 (51.2)	10 (23.3)	24 (55.8)	1 (2.3)
Component of a complex intervention	31 (32.3)	18 (58.1)	11 (35.5)	14 (45.2)	1 (3.2)

*Percentages do not add up to 100 due to the possibility of multiple tools and multiple objectives per study.

Table 4.4. Social media tools by user group

User group	Total – n (%)	Collaborative project – n (%)	Blog or microblog – n (%)	Content community – n (%)	Social networking site – n (%)	Virtual world – n (%)	Discussion forum – n (%)
Discipline							
Education	66/96						
Allied health	10 (10.4)	2 (20.0)	-	1 (10.0)	1 (10.0)	-	6 (60.0)
Dental/dental hygiene	5 (5.2)	1 (20.0)	3 (60.0)	1 (20.0)	-	-	-
Interdisciplinary	6 (6.3)	1 (16.7)	2 (33.3)	-	2 (33.3)	1 (16.7)	4 (66.7)
Medicine	22 (22.9)	4 (18.2)	3 (13.6)	3 (13.6)	2 (9.1)	2 (9.1)	12 (54.5)
Nursing	17 (17.7)	1 (5.9)	1 (5.9)	1 (5.9)	-	2 (11.8)	12 (70.6)
Pharmacy	3 (3.1)	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	-
Public health	3 (3.1)	-	2 (66.7)	-	-	1 (33.3)	1 (33.3)
Practice	18/96						
Allied health	3 (3.1)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	-	2 (66.7)
Interdisciplinary	3 (3.1)	2 (66.7)	2 (66.7)	1 (33.3)	1 (33.3)	-	-
Medicine	7 (7.3)	2 (28.6)	3 (42.9)	3 (42.9)	3 (42.9)	-	1 (14.3)
Nursing	2 (2.1)	-	-	-	-	-	2 (100)
Pharmacy	3 (3.1)	-	2 (66.7)	-	-	-	1 (33.3)
Public health	2 (2.1)	-	1 (50.0)	-	1 (50.0)	-	1 (50.0)
General	10/96						
Accuracy, online presence, perceptions, etc.	10 (10.4)	3 (30.0)	6 (60.0)	1 (10.0)	4 (40.0)	2 (20.0)	1 (10.0)
Specialty							
Common specialties							
Administration, critical appraisal, and research	11 (11.5)	5 (45.5)	5 (45.5)	2 (18.2)	4 (36.4)	3 (27.3)	6 (54.5)
Cardiovascular	3 (3.1)	-	-	1 (33.3)	-	1 (33.3)	1 (33.3)
Dentistry	4 (4.2)	1 (25.0)	2 (50.0)	1 (25.0)	-	-	-
Geriatric medicine	2 (2.1)	-	-	-	-	1 (50.0)	1 (50.0)
Internal medicine	2 (2.1)	-	1 (50.0)	-	1 (50.0)	1 (50.0)	-
Mental health	6 (6.3)	-	1 (16.7)	1 (16.7)	1 (16.7)	-	5 (83.3)
Pediatrics	2 (2.1)	-	-	-	1 (50.0)	-	-
Primary care	3 (3.1)	1 (33.3)	-	1 (33.3)	-	-	2 (66.7)
Public health	9 (9.4)	2 (22.2)	3 (33.3)	-	1 (11.1)	2 (22.2)	3 (33.3)
Radiology	3 (3.1)	1 (33.3)	-	1 (33.3)	-	-	1 (33.3)
Rural medicine	2 (2.1)	-	-	-	-	-	2 (100)
Spanning multiple specialties	33 (34.4)	8 (24.2)	12 (36.4)	6 (21.2)	7 (21.2)	2 (6.1)	12 (36.4)

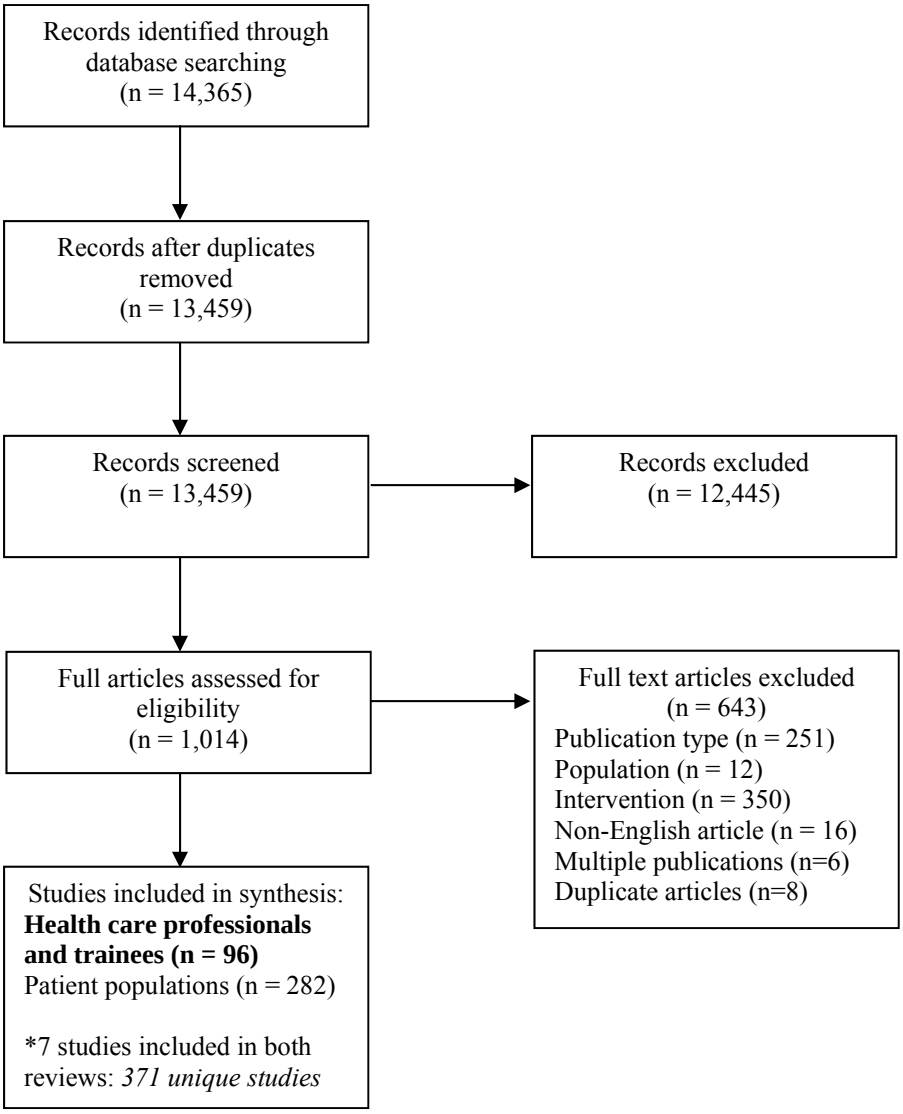
*Percentages do not add up to 100 due to the possibility of multiple tools per study

Table 4.5. Outcomes measured by social media tool

Social media tool	Total – n (%)	Excluding discussion forums – n (%)	Collaborative project – n (%)	Blog or microblog – n (%)	Content community – n (%)	Social networking site – n (%)	Virtual world – n (%)	Discussion forum – n (%)
Total – N	***96***	***53***	***20***	***27***	***13***	***16***	***9***	***43***
Clinicians' knowledge								
Conditions and complications	22 (22.9)	12 (22.6)	4 (20.0)	6 (22.2)	3 (23.1)	4 (25.0)	2 (22.2)	10 (23.3)
Treatment options	4 (4.2)	3 (5.7)	1 (5.0)	-	-	1 (6.3)	1 (11.1)	1 (2.3)
Comprehension	19 (19.8)	7 (13.2)	3 (15.0)	3 (11.1)	1 (7.7)	-	1 (11.1)	12 (27.9)
Recall	4 (4.2)	2 (3.8)	2 (10.0)	-	-	-	-	2 (4.7)
Clinicians' experience								
Satisfaction	36 (37.5)	16 (30.2)	7 (35.0)	4 (14.8)	4 (30.8)	2 (12.5)	2 (22.2)	20 (46.5)
Peer-to-peer communication	43 (44.8)	19 (35.9)	5 (25.0)	11 (40.7)	5 (38.5)	6 (37.5)	3 (33.3)	24 (55.8)
Instructor-student communication	17 (17.7)	5 (9.4)	2 (10.0)	1 (3.7)	2 (15.4)	-	1 (11.1)	12 (27.9)
Clinician-patient communication	9 (9.4)	6 (11.3)	3 (15.0)	4 (14.8)	4 (30.8)	5 (31.3)	-	3 (7.0)
Clinician-public communication	9 (9.4)	9 (17.0)	1 (5.0)	7 (25.9)	2 (15.4)	3 (18.8)	1 (11.1)	-
Professional behaviour								
Skills	17 (17.7)	8 (15.1)	2 (10.0)	1 (3.7)	1 (7.7)	1 (6.3)	3 (33.3)	9 (20.9)
Guideline adherence	1 (1.0)	1 (1.9)	1 (5.0)	-	-	-	-	-
Boundaries	5 (5.2)	5 (9.4)	1 (5.0)	3 (11.1)	1 (7.7)	3 (18.8)	1 (11.1)	-
Other								
Content and accuracy	6 (6.3)	6 (11.3)	3 (15.0)	2 (7.4)	1 (7.7)	-	-	-
Usability	15 (15.6)	6 (11.3)	3 (15.0)	4 (14.8)	1 (7.7)	2 (12.5)	1 (11.1)	9 (20.9)
Usage and demographics	19 (19.8)	13 (24.5)	6 (30.0)	10 (37.0)	7 (53.9)	9 (56.3)	3 (33.3)	6 (14.0)

*Percentages do not add up to 100 due to the possibility of multiple outcomes per study

Figure 4.1. Flow diagram of included studies



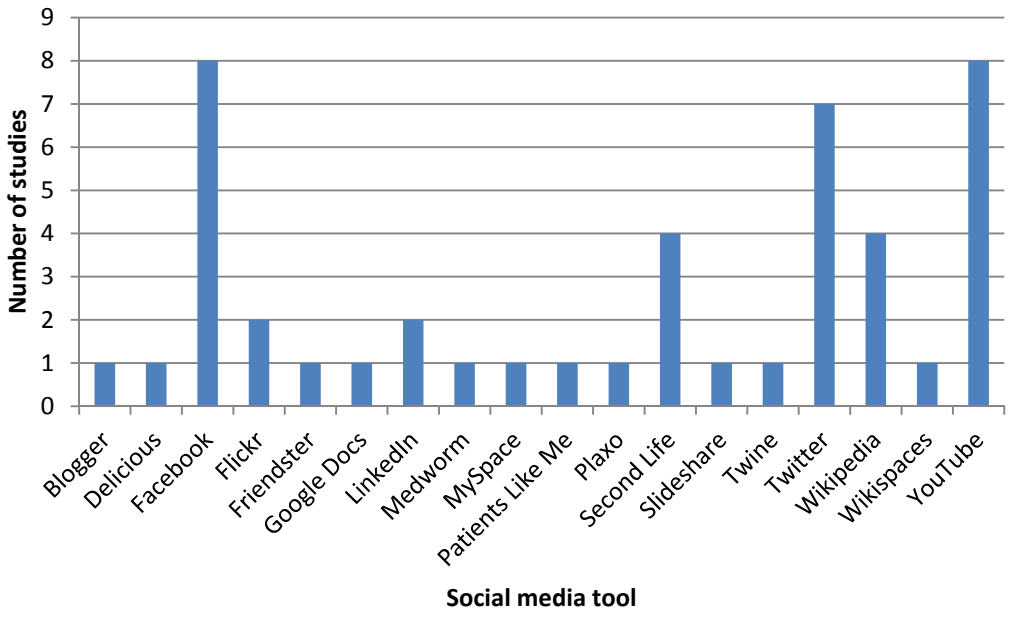


Figure 4.2. Specific social media tools described in included studies

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Chapter 5

Improving health research methodology: pilot test of a wiki as a novel knowledge translation intervention[4]

Michele P Hamm, Terry P Klassen, Shannon D Scott, David Moher, Lisa Hartling

5.1. Introduction

Knowledge translation (KT) strategies for delivering education and professional development to health care providers are of great interest in optimizing health services and delivery. The Effective Practice and Organisation of Care (EPOC) Review Group within The Cochrane Collaboration has been particularly instrumental in synthesizing the evidence and evaluating the effectiveness of interventions aimed at improving the delivery, practice, and organization of health services, including in continuing education and quality assurance.[1] Traditional KT interventions that have demonstrated effectiveness in EPOC systematic reviews include printed educational materials (4.3% absolute improvement in categorical process outcomes versus no intervention),[2] combining didactic and interactive content in the distribution of educational materials (13.6 median adjusted risk difference (RD) in outcomes for professional practice versus didactic (RD 6.9) or interactive (RD 3.0) sessions alone),[3] and endorsement by local opinion leaders (12% median absolute increase in compliance in behaviour versus no intervention, an alternative intervention, or multiple alternative interventions).[4] While extensive research has been conducted with respect to changing clinician behaviour, the impact of KT strategies on researchers' behaviour has not been explored to date.

There is a body of evidence suggesting that pediatric randomized controlled trials (RCTs) are susceptible to methodological limitations, and a substantial proportion of the studies conducted are at a high risk of bias,[5-14] increasing the likelihood that

[4] *A version of this chapter has been submitted for publication. Hamm et al. Medical Teacher.*

treatment effects are being exaggerated. Guidance on rigorous trial conduct and reporting is available in abundance,[15-25] as is research on specific challenges inherent to trials in child health.[26-30] However, a research-practice gap persists between what is known about bias and how RCTs are conducted, indicating a need for KT research in this population.

In previous work investigating the barriers and facilitators to the uptake of methodological principles in child health research, pediatric trialists indicated that a lack of formal training in research methods and a negative research culture adversely impacted their ability to conduct RCTs to the highest standards, while contact with knowledgeable and supportive colleagues had a beneficial effect.[31] In this context, we endeavored to develop a KT intervention for researchers that would be tailored to address these factors.[32]

Social media tools have recently begun to be explored as KT interventions in educational contexts.[33] Wikis, collaborative websites that can be edited by all users,[34] provide a unique opportunity to build on existing KT research and to be used as novel tools in disseminating information. Due to the flexibility in their formatting, wikis can be created to incorporate a number of successful elements of other strategies, such as interactivity alongside static educational content and involvement of opinion leaders. Additionally, a wiki could act as a centralized resource centre for materials related to trial methodology, while promoting a positive research culture and providing a supportive online community, in response to the key factors identified by researchers in the field. There are a few existing models of wikis that have been used to disseminate methods research,[35,36] but their use is not yet widespread.

The objective of this study was to develop and pilot test a wiki designed to educate child health trialists and trainees in the principles involved in minimizing risk of bias in RCTs.

5.2. Methods

5.2.1. Wiki development

The wiki was developed using Wikispaces, a free host platform.[37] In order to maximize credibility and familiarity, the wiki was established under the auspices of StaR Child Health, an international initiative dedicated to improving the quality of pediatric clinical research,[38] and is available at www.starchildhealth-riskofbias.wikispaces.com. Specifically, the wiki was designed to contribute to the KT agenda of the StaR Child Health Risk of Bias Standard Development Group.[39] Content was structured to emphasize two main areas: risk of bias and the conduct of pediatric RCTs. Guidance on minimizing risk of bias followed the framework developed by The Cochrane Collaboration and was focused on seven key domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.[40] Overall, the wiki comprises six major sections: an introduction, a page for each of the risk of bias domains including resources and interactive examples, issues specifically relevant to pediatric trials, a discussion forum, tools, and references.

Development of the wiki followed the three main steps of tailoring interventions: 1) identification of the barriers and facilitators faced by the target users; 2) matching the intervention to the identified factors; and 3) applying and assessing the tailored intervention.[41] A theoretical foundation was also applied, drawing on Diffusion of Innovations[42] to outline the key attributes of innovative ideas or technologies (relative advantage, compatibility, complexity, trialability, observability) and focus theory of normative conduct,[43] which states that motivation for behavioural change can arise through emphasis on what ought to be done (i.e., encouraging rigorous trial conduct) versus what is done (i.e., highlighting the prevalence of poorly conducted trials). Several KT strategies were incorporated into the wiki design, interactivity prominent among them. Much of the educational content is intended to be static, but this appears alongside interactive components, including examples that users can work through,

discussion forums, editing capabilities, and social media (Twitter feed). The wiki has been endorsed and promoted by key members of StaR Child Health, who are recognized leaders in the fields of pediatrics and trial methodology. Technological elements and formatting of the wiki were informed by the U.S. Department of Health and Human Services' (HHS) guidelines on web design and usability.[44]

5.2.2. Target audience and recruitment

The target audience for the wiki pilot test consisted of both clinical trialists, to ensure relevance of content, and methodologists, to ensure accuracy. Participants were recruited from three sampling frames: students enrolled in systematic review and randomized controlled trials courses, pediatric trialists, and methodologists affiliated with the Agency for Healthcare Research and Quality Evidence-based Practice Center Program. Recruitment occurred between March and June 2012 through presentations to groups of trainees, promotion at prominent pediatric and methodological conferences, and targeted email requests. This study was approved by the Health Ethics Research Board at the University of Alberta.

5.2.3. Data collection

To evaluate the usability of the wiki, we conducted semi-structured interviews that were based on the major constructs identified in the HHS guidelines: user perceptions of consistency, efficiency, productivity, organization, ease of use, intuitiveness, and straightforwardness.[44] User preferences regarding content and formatting were ascertained to inform the modification of the prototype version of the wiki (Appendix Q). We aimed to conduct approximately 12 interviews to reach saturation. Each participant signed and returned a consent form prior to the conduct of the interview (Appendix P). Interviews were 30 to 60 minutes and conducted in person or by telephone by the first author (MPH). All interviews were recorded and transcribed verbatim.

Quantitative measures of web traffic were collected, both through the usage statistics built into the Wikispaces platform, and through Google Analytics.

Measures included number of unique visitors, geographic location, and page views.

5.2.4. Data analysis

We used directed content analysis to code interviews,[45] identifying categories in the data that described usability, user preferences, and feedback for modification and improvement (Appendix R). The lead author coded the data in consultation with the rest of the study team. We conducted qualitative data collection and analysis concurrently, following an iterative process.[46] We used NVivo to manage qualitative data. Quantitative data is presented descriptively, using frequencies and proportions.

5.3. Results

The wiki was pilot tested with 15 participants, at which point saturation was reached. Four were trained as physicians, six were PhD-trained researchers, four were PhD students, four were masters-trained researchers (including project coordinators), and one was entering a masters program (research assistant). Six participants specialized in pediatrics, seven had experience conducting RCTs, and nine had experience conducting systematic reviews. Three were new to the concepts of risk of bias. Thirteen were from Canada, one was from the United Kingdom, and one was from the Netherlands. An outline of the design of the wiki is provided in Appendix S and screen shots are included in Appendix T.

5.3.1. Usability

All of the participants found the wiki to be well organized, easy to use, and straightforward to navigate (Table 5.1). The simplicity of the site was seen as a strength, and it was found to be logical and user-friendly. Respondents liked the layering of the wiki, with its focus on general and introductory content, with links and references to more detailed or complex information. The content and language was easy to understand, with only minor suggestions for clarification. While much of the background information included in the wiki is available

through other sources, participants liked that the site provided a centralized collection of this content, making it easier to find and work through.

5.3.2. User preferences

Participants liked the additional features of the site that were supplementary to the text and wanted to see more added in (Table 5.2). In particular, they liked case studies and real world illustrations, interactive polls that served as teaching examples, diagrams, and the Twitter feed. The polls were structured to provide an excerpt from a published trial and the user could assess the example as being at low, unclear, or high risk of bias. Their responses would then be presented along with those of other users. Although we deliberately did not include a 'correct' answer due to the inherent subjectivity of the assessments, many participants felt that this would have been helpful. One respondent felt that allowing for voting took away from the credibility of the site.

While users liked the example polls, they found that they caused the pages to load slowly, which was a significant disadvantage (Table 5.2). There was an interesting contrast in the comments between wanting to maintain the simplicity of the site and suggesting the addition of more technologically advanced features, such as in the presentation of the examples, the use of tabs for navigation, and creating links within figures. This difference tended to run across generational lines, with younger participants more at ease with a wider range of digital functionality.

5.3.3. Audience

Given the use of The Cochrane Collaboration's framework for risk of bias to structure the wiki, there was some uncertainty regarding the intended audience, specifically whether it was targeted for trialists or systematic reviewers and whether the connection between assessing risk of bias in a published study and addressing it in the design and conduct of a trial would be apparent.

> "I think it has to be clear somewhere [...] that risk of bias is not a guideline for conducting a trial, it's just highlighting some elements that will enhance the quality, internal validity of the study, and so on." – *08 (systematic reviewer)*

Suggestions were made to add more tools that focused on the pragmatic issues related to conducting an RCT to increase the site's relevance to trialists. Resources on the wiki such as tips on how to blind surgical trials were viewed as being useful, and participants wanted to see more tools like these. Other comments were focused on tailoring information to different user groups. With potential applications for trialists and systematic reviewers or methodologists, participants suggested that it could be useful to either divide content into sections that would be most relevant to different groups, or to provide a framework up-front explaining how different users should make use of the site.

5.3.4. Web traffic

Over the study period (May 3 – July 5, 2012), 240 unique visitors accessed the wiki. Nearly all visits were from Canada (87.6%), followed by the United Kingdom (2.7%), the United States (2.4%), and the Netherlands (1.8%). The most highly accessed pages within the wiki were the domain-specific pages for sequence generation and allocation concealment and the comprehensive tools page, compiling the tools and resources for all of the risk of bias domains. The pages that were intended to encourage interactivity, namely the pediatric-specific issues and discussion pages, were accessed 11th and 12th most frequently, respectively, out of 40 pages. There were, however, no contributions to any of the discussion forums.

5.4. Discussion

Overall, the feedback on the risk of bias wiki was positive, with participants viewing this method of dissemination favourably. Suggestions for improvement were largely related to issues of clarification or esthetics, rather than the content,

format, or usability. Participants were interested in the opportunities provided by the wiki as a relatively novel educational tool, and felt that this platform held potential for future uses in providing methodological training.

One of the concerns related to using a wiki in the educational realm is that there is no guarantee that the content will be accurate because it can be modified by any wiki user without editorial control.[34,47-48] However, only one respondent in our study voiced this opinion, stating:

> "So what I don't understand is you have this wiki to teach people? I think that's one of the aims? But at the same time, you allow them to edit what's in there – isn't that a bit dangerous? If somebody goes to this wiki and puts in nonsense?" – *10 (trialist)*

This will be an important consideration not only in the authenticity of the wiki content, but also in the site's sustainability, as it will have implications for the resources required if ongoing monitoring is necessary. A certain level of continued involvement on the part of the developers can be expected, but there is some evidence that online information tends to be self-correcting,[49] and with many wiki users preferring to act as passive knowledge consumers, rather than as active editors,[50] this may not represent a significant issue.

Obtaining buy-in for the wiki from the target end-users will represent a substantial challenge. Not only are there barriers in terms of encouraging participation once the site has been accessed, but the intended audience of pediatric clinical trialists already faces significant time constraints and is largely part of an environment in which education on research methodology is not highly valued.[31] The use of theory, established KT strategies, and tailoring in the development of the wiki were used to mitigate these obstacles, but do not overcome the challenge of drawing users to the site. The ideal use of a wiki would likely be in the context of a course or training module in which users are motivated or required to

participate, in which case it could potentially parallel the successes found in the use of online continuing medical education, where benefits have been found in knowledge gains and in changing clinician behaviour.[51,52] Additionally, this strategy would align with evidence that multifaceted interventions targeting change are more effective than single interventions.[53]

While the KT literature that this study was based on is focused on changing clinician behaviour, it lends itself to adaptation to the target population of trialists, as most are clinician scientists. However, their motivation to change may differ when choosing whether to adopt a new or recommended clinical practice versus a research technique with more subtle or distant benefits. With a lack of available empirical evidence, theory can be used to outline potential strategies to address such challenges. Social influences theories guided our approach to targeting motivation, specifically the contrast between descriptive norms (what is done) and injunctive norms (what ought to be done) emphasized in the focus theory of normative conduct.[43] In future promotion of the wiki, social influence could also play a role by continuing to engage respected opinion leaders.

This prototype wiki was developed specifically as a resource for the Risk of Bias Standard Development Group within StaR Child Health, but it can also potentially serve as a model for resources targeting other key areas in pediatric research, for example, data monitoring committees and recruitment. One of the aims of StaR Child Health is to be at the forefront of guidance for trial design, conduct, and reporting in pediatric research,[38] and a series of wiki-based educational resources could contribute to this vision. This pilot study represents the first step in the evaluation of this intervention, and the revised version of the wiki will need to be further evaluated for effectiveness. If shown to be beneficial, an implementation strategy will be devised.

5.5. Limitations

The majority of participants in this study were more experienced in systematic reviews than in RCTs. While this did confer an advantage in that they tended to be familiar with the Cochrane Risk of Bias tool and could provide feedback on the accuracy of the content, there was more feedback related to how to improve the site for reviewers than on what could be useful to trialists. Moving forward, however, the guidance on methodology has been found to be sound, and therefore seeking the input of clinical researchers on relevance can be emphasized in future evaluations.

Nearly all of the comments on the usability of the wiki were positive, raising the question of the possibility of bias. However, participants were forthcoming with ideas to improve the layout of the site and for additions that could strengthen the content in the future, suggesting that they did not feel compelled to provide only positive feedback.

There were a number of suggestions for modifications based on incorporating more advanced technology into the wiki. A standard website would allow for more flexibility than a wiki in the inclusion of functions that would streamline the site. However, this would be at the cost of the interactivity that the wiki affords and we felt that a less sophisticated site held more potential as an educational resource due to the user-generated components it supports.

5.6. Conclusions

This pilot study was designed to evaluate the usability of a wiki-based educational resource on methodological rigor in pediatric randomized trials. Participants found the wiki straightforward and easy to use, providing suggestions to improve clarity and esthetics. The interactive format was enticing to users and the components that allowed participation or emphasized practical applications over theory were preferred. Built upon an adaptation of the existing knowledge translation evidence base, the risk of bias wiki holds promise for use as an online educational resource for trialists in child health.

Table 5.1. Typical comments on the usability of the wiki

07 (trialist, systematic reviewer) – I thought everything was really easy to read and easy to follow and not too scientific, like I could follow everything. *11 (trialist)* – Navigation was quite easy. So I did find myself, you know, you'd be reading from the home page and then click in to get to more information, and then I'd click on something else – so I'd get myself off track and off the home page, but that was just my own personality, or the way I navigate a page, but it was nice to be able to go deeper and deeper. It did take me away from the text, but I was always able to get back to the home page quite easily, so that was good. *11 (trialist)* – I think that if people wanted the quicker view, you could stick to the home page, and then you know, if you find the details excessive, then people don't have to click into the extra text in each side heading. So no, I think that the way it was organized gave either a brief overview or more in-depth – I think the choice was useful. *09 (trialist, systematic reviewer)* – It did strike me as a nice centralized place to have all that information. Most of it, as far as I can tell, is out there somewhere; the question is finding it all in one place. I thought that was good there.

Table 5.2. Typical comments on user preferences

Supplementary features
16 (psychologist) – I clicked on a couple of the links to the Twitter leads as well. And that's quite nice, because that gives sort of a current flavor, [...] real-world things that people are talking about. *03 (project coordinator)* – I really like this [case study from a medical drama storyline]. This was, for me, tied in to pop culture – like what are most people familiar with? You could relate to it, and it's a clear example right there. So it's not just a whole lot of theory. And I think that's why the polls were kind of nice as well. *16 (psychologist)* – ... real life examples that happen quite commonly in clinical trials. I think that's quite nice. It's one thing to learn about in the abstract, but when you know that it's happened in the real world, it's a real thing that can happen and that you need to watch out for this, I find that's quite powerful.
Example polls
03 (project coordinator) – [The examples were] a really interactive way for people to actually sit down, like for me not to know a lot about risk of bias, and be learning it on the go, and you don't have to do a lot to learn piece by piece. Like if I had to go do something else, then I could still go back to it and pick away at it, [...] then you don't feel like it's too intensive. *01 (trialist, systematic reviewer)* – But does it tell you whether you're right or wrong in the end? *14 (trialist, systematic reviewer)* – I answered the poll, and then you sort of see how other people have answered the poll. But maybe that's just me being sort of scholastic, but I'd be sort of curious about what the answer is. But I don't think there is an answer, is there? And then the more I thought about it, I think that's the point, is that you know, two really smart people could answer the same question different ways, and not necessarily one of them is right or wrong. *10 (trialist)* – To see votes, I mean it's like a beauty contest or something like that [...] and it's not very attractive, I think, to people who want to do serious scientific

work.

Technological features

13 (research assistant) – To me, it wouldn't be as big of a deal to have [the text of the examples separated from the polls in a less esthetically pleasing format] than to have the page slowed down [by large text boxes].

14 (trialist, systematic reviewer) – I noticed that it was slow every time I was on it.

12 (systematic reviewer) – I like the fact that everything – it's not overwhelming. I'm not much for websites with lots of bells and whistles, so I like the fact that it's not overwhelming, but it's not bland either.

16 (psychologist) – I think one of its beauties is its simplicity.

13 (research assistant) – I thought it would be cool [...] if you could have the [risk of bias] guidelines move along down the page [beside the examples while scrolling].

01 (trialist, systematic reviewer) – I know this is an over-simplification of the whole process, but people tend to like wizards. Where you're asked a question and you say for example, "was this study randomized?" Or "will this study be randomized?" And then they say yes or no, and then based on that, you get a second question and so on. And at the end they would get their answer.

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Chapter 6
Discussion

6.1. Overview of findings

This series of studies was designed to address the quality of pediatric randomized controlled trials, the barriers and facilitators that exist in conducting child health research, and the development of a strategy to improve methodological rigor in this area. Building incrementally upon each other, these phases have provided a foundation which can be used to increase awareness and promote the uptake of the principles of evidence-based medicine and risk of bias among pediatric trialists.

6.1.1. Quality of pediatric randomized controlled trials

Overall, the quality of recently published pediatric randomized controlled trials was poor, with nearly all studies at unclear or high risk of bias. This finding is consistent with numerous other reports and suggests that regardless of the clinical area studied, and despite the introduction of initiatives such as the CONSORT Statement and prospective trial registration to improve methodological rigor, there remains a discrepancy between what is and what ought to be done. As well as being consistent with the published literature, the poor assessment of quality was consistent across the different tools used, including The Cochrane Collaboration's Risk of Bias tool, the Jadad score, and the CONSORT checklist.

We found that there was a trend linking the risk of bias of a trial to the magnitude of the effect estimate of the primary outcome. The implications of trials at high risk of bias presenting higher effect sizes than those at low risk of bias include the potential for publication bias, incorrect interpretation of study results, and flawed clinical decision making. As this is an issue that continues to persist and ultimately has the potential to influence health-related outcomes, it is clear that improved dissemination of methodological principles is necessary.

The promotion of trial registration has begun to make some progress as a strategy to improve trial methodology. Since its endorsement by the International Committee of Medical Journal Editors in 2005, there has been a continuous increase in the number of trials prospectively registered,[1,2] although gaps remain to be filled. In our study, a low proportion of trials was registered, but those that were registered were more likely to be at low risk of bias than trials that were not registered. As the expectation that trials must be available in a registry grows, this could potentially contribute to an increased awareness of at least some of the issues that are relevant to minimizing bias in an RCT. This sentiment is mirrored in the increased adoption of the CONSORT Statement.[3] While reporting cannot be a perfect proxy for study conduct, quality assessment depends heavily on the details that are included in the publication.

Since this study was published, The Cochrane Collaboration has updated and slightly modified its Risk of Bias tool.[4] Blinding was originally considered within one domain and it has now been split into two: blinding of participants and study personnel and blinding of outcome assessment. Additionally, the influence of the study sponsor is no longer used to inform the assessment of "other" sources of bias. While it is unknown exactly how these new criteria would impact the study findings, a likely result would be that fewer trials would have been assessed as low risk of bias for blinding, since studies that reported blinding either the participants and personnel or the outcome assessors would have been given credit while they may not meet the criteria for both of the new domains; and the proportion of trials assessed as high risk of bias for "other" sources of bias would decrease, since industry funding was a large driver for the original judgments.

6.1.2. Barriers and facilitators in conducting child health research

The major barriers to methodological rigor in RCTs that were identified by pediatric trialists included a lack of knowledge of research methods, maintaining the distinction between clinical care and clinical research, a negative research culture, logistics, and administrative constraints. While the logistics of running a

trial and the administrative demands may depend on organizational and systemic structures that are not easily changed, the remaining barriers can potentially be addressed through education at the individual level. Most trialists lack formal training in research methodology, and they practice in an environment in which there is very little value placed on conducting research. By increasing the accessibility of training opportunities, encouraging mentorship, and emphasizing the importance of integrating research with clinical practice, the perceived value of research methodology may rise.

While the barriers to methodological rigor may be addressed through a focus on education, the facilitators tended to focus on the quality of relationships and the availability of resources. Respondents identified having a sense of ownership of the trial, acceptance within the clinical setting, belonging to a cohesive study team, established research infrastructure, and verification processes as facilitating trial conduct. Drawing on these factors to inform knowledge translation activities would suggest that fostering a sense of community is important in ensuring positive working relationships in which different stakeholder groups (i.e., clinicians and researchers) are receptive to the needs and priorities of others.

6.1.3. Development of a strategy to improve methodological rigor

By their nature, knowledge translation strategies are intended to be adaptable to the needs and preferences of their target audience. Given the popularity and widespread use of social media, we investigated its use as a dissemination tool. In our scoping review of the uses of social media by health care professional and trainee populations, we found that these applications are being widely studied for their ability to facilitate communication, aid in the creation and transfer of knowledge, and refine the development of clinical skills. The largest proportion of included studies used social media tools for the purposes of education, rather than to contribute to health care practice, and the most commonly used platforms were blogs or microblogs and collaborative projects.

Collaborative projects, which include wikis, allow users to add, remove, and change content,[5] all within a format that allows a great deal of versatility. In a wiki, static materials can be posted alongside dynamic, user-generated content, providing variety in educational tools, accounting for different individual learning styles, and offering a sense of user ownership over the direction that knowledge use will take. Given these factors, we decided to develop a wiki as an educational resource on issues related to bias in pediatric RCTs.

Our pilot test focused on the usability of the wiki, both in terms of the content and the format of the site. Minor comments were made to clarify some of the statements included within the site and to improve the esthetics, but overall, participants were satisfied with the concept of using a wiki to disseminate methodological guidelines. In particular, components that were supplementary to the main text were received favourably, including case studies and examples. While in this preliminary stage examples are still being collected to include in the wiki, one of the primary goals of using this type of tool is to provide a platform where users can post their own experiences as examples, allowing the opportunity to ask questions, generate discussion, and educate others. By shifting from a one-way transfer of information to a collaborative setting in which users play a role in dissemination, the hope is to increase the relevance to stakeholders, thereby increasing the likelihood that the resource will be used and the practices regarding bias in trial design will be adopted.

Drawing from the concepts embodied within the EPOC framework of knowledge translation interventions, several other options were considered as potential dissemination tools, including a standard website, mobile and social media applications, and a protocol review system (Appendix U). While each of these modalities could be adapted to meet the intended purpose of disseminating methodological guidelines, a wiki was chosen as the best fit for the message and target audience. By allowing for large amounts of content to be posted, layering the amount of detail that could be explored, including interactivity, and being

relatively self-sustainable, we felt that a wiki would be the most compatible with the aim of providing an educational resource for a professional group with varying levels of time, interest, and experience related to research methodology.

6.2. Future research

The risk of bias wiki was developed as a prototype and will require further evaluation. While a first round of pilot testing has been conducted as part of this study, the development of a resource like this is an iterative process and depends on a cycle of revisions based on user feedback. Preliminary work evaluating the effectiveness of the site as a learning tool was conducted by an independent group and interim results suggested that scores on tests of knowledge were similar between groups that were provided with access to the wiki and that were provided with standard in-person instruction. However, the feedback provided by participants in the initial pilot test had not yet been incorporated into the wiki, therefore there is room to build upon the existing foundation and evaluate the modified version.

Evaluation of the effectiveness of the wiki in increasing knowledge about risk of bias will be an important next step. This could be incorporated into a workshop, or more ideally, into a classroom setting in which RCT methodology is being taught. A cluster RCT design could be used, randomizing classes into two groups: the control group to receive classroom teaching alone and the intervention group to receive classroom teaching supplemented with access to the wiki. Using at least two separate classes running simultaneously would minimize the potential for contamination. However, while this design may provide the highest strength of evidence, in practice, it would likely be underpowered to detect an effect due to the logistics of recruiting eligible classes. A similar concept could be evaluated through the use of a controlled before-after design. Over the course of at least two years of offering a course in RCT methodology, classes from two different institutions could comprise the intervention and control groups. In the first year, both groups would receive standard, in-class teaching, which would then be

supplemented by the availability of the wiki as a resource for the intervention group in the second year. Assessment each year would be based on: 1) the development of a protocol for an RCT, a typical term assignment in this type of course, appraised using the Cochrane Risk of Bias tool; 2) a test of knowledge, using a multiple choice exam, at both the beginning and the end of the term; 3) web traffic using Google Analytics to allow for correlations between time spent on the site and performance in the class; and 4) a course evaluation, including measures of satisfaction. While assessing protocols for risk of bias would provide the most direct measure of the uptake and application of the methodological principles taught, the ability of the Risk of Bias tool to meaningfully differentiate between the knowledge gains between learners may be limited due to its use of only seven domains. A complementary multiple choice exam would therefore enhance the evaluation process. Additionally, the use of a pre-post test design for the exam would allow for both within- and between-group comparisons.

In the longer term, it will be interesting to investigate whether any uptake of knowledge regarding trial methodology translates into improved RCT design and conduct. One way to do this would be to link the wiki to the ethics review process within institutions across Canada and assess the quality of submitted protocols, or eventually, published pediatric clinical trials. Using a cluster randomized design in which institutions were randomly assigned to be able to access the wiki as a resource in the protocol submission process or to follow standard procedures would allow for a comparison of how well methodological concepts are put into practice. In the classroom scenario described above, knowledge and comprehension of principles could be measured, but this would only be an indicator of intended behaviour, likely an overestimate of actual behaviour. Evaluation of submitted protocols would also be a measure of intended behaviour, but would presumably show a closer correlation between intention and action, as the submitted protocols would be developed for real-world application, rather than as a class assignment. The best measure of study quality would be from completed trials; however, this would require an extensive follow-up period to

allow for the time necessary to conduct and publish the studies of interest, and would provide the most opportunity for the dilution of any effect attributable to the intervention.

If shown to be beneficial, the use of the wiki could be extended to training in research methodology, for example through workshops, to endorsement by research networks such as the Maternal Infant Child and Youth Research Network in Canada, and to other topic areas within StaR Child Health. Workshops and research networks are important sectors to target due to their role in providing resources for trainees and new investigators. Targeting these user groups will likely have the greatest impact, as seen through the adoption of new research practices. These types of venues would also have the potential to be inter-disciplinary, facilitating the uptake of rigorous methodology by the diverse range of end-users that participate in conducting pediatric RCTs (e.g., physicians, nurses, psychologists).[6] While the wiki was developed specifically to correlate with the aims of the Risk of Bias Standard Development Group within StaR Child Health, there are numerous other Standard Development Groups in which an online resource could be developed, modelled after this tool. In this way, a suite of educational resources could be compiled under the StaR Child umbrella, contributing to its ability to be at the forefront of guidance on all aspects of pediatric trial design, conduct, and reporting.

The role of gatekeepers in the research process should also be considered in future knowledge translation initiatives. Parallel to the role that journals play in endorsing reporting guidelines, bodies such as funders, research ethics boards, and trial registries could be influential in determining whether trials have been designed to meet appropriate methodological standards. Each group has a vested interest in ensuring that the research that is conducted is done to the highest quality, whether it's the return on investment, the unethical nature of subjecting participants to research that is uninformative or unnecessary, or the value placed on transparency. A resource that provides a map for proper trial conduct could be

endorsed as a contributing factor to addressing all of these concerns. The SPIRIT Initiative (Standard Protocol Items: Recommendations for Interventional Trials)[7] has focused on establishing a comprehensive list of items that should be included in the protocol for an RCT and has been engaging these very stakeholders in the process.[8] Due to the overlap in aims between the SPIRIT group and the Risk of Bias Standard Development Group, potential for collaboration should be explored.

The sustainability of the wiki as an educational resource will need to be considered. While much of the work occurs up-front in the development stages, the intention is to encourage ongoing contributions from users; therefore a certain level of monitoring will be required. Depending on the evolution of this tool as a knowledge translation intervention, the interest or involvement of different user groups may create a shared sense of responsibility for maintaining the accuracy and functionality of the site.

6.3. Strengths and limitations

This study has used an integrated approach to involving the target end-users in all aspects of developing an educational tool to be used in the design of pediatric RCTs. By involving pediatric clinical trialists in the identification of the barriers to be addressed in a knowledge translation intervention, and by seeking their input on a prototype version of that intervention, it is more likely that the tool will be relevant to end-users and that the ideas put forth will be adopted.

A mixed methods approach provided both depth and breadth to the study findings and has allowed for a more detailed picture to emerge regarding trialists' awareness of bias, the factors that influence their ability to address bias in the conduct of RCTs, and their preferences for strategies to minimize the influence of bias in pediatric research. The incorporation of multiple sources of data adds to the robustness of the results, combining the richness and the generalizability of the qualitative and quantitative findings, respectively.

The survey response rates were relatively low (50% for trial registration; 23% for barriers and facilitators), calling into question the external validity of the results. It is likely that respondents were more interested or experienced in research methods than non-respondents, introducing a response bias. However, they also represented a diverse range of subspecialties, geographic locations, and training backgrounds, providing insight into the broad spectrum of pediatric clinical research.

Introducing a degree of separation in the wiki pilot test interviewers between the site developer and the interviewer may have been beneficial. As I was the one in both roles, interview participants may have felt that there was some pressure to give positive feedback. While suggestions for improvement to the wiki were encouraged, there may have been more perceived freedom to speak candidly if another interviewer had been involved instead.

6.4. Conclusions

This series of studies has linked empirical data on the quality of pediatric randomized controlled trials; barriers and facilitators to methodological rigor, as identified by trialists in child health; and the development and initial evaluation of a knowledge translation intervention to be used to minimize bias in pediatric research. This work contributes to the evidence base on the methods used in pediatric RCTs and serves as a foundation for future knowledge translation research targeting clinician-scientists.

Further modifications and evaluation of the risk of bias wiki will be necessary before it is known whether or not it will be useful to trialists, but the preliminary findings are promising. With a substantial body of literature documenting the methodological issues in pediatric RCTs, the recognition that formal training initiatives can benefit research in the longer term, and the popularity of social

media in medical education, the wiki is well positioned to become a valuable resource to researchers.

Improvement in the quality of pediatric randomized controlled trials is needed, and this work provides insight into a knowledge translation intervention that may be used as a tool to contribute to this end goal. By informing how best to maximize the value of child health trials, this strategy can help to optimize therapeutic decision-making and to improve patient outcomes.

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Chapter 7
Conclusions and Recommendations

7.1. Conclusions

Based on the findings reported in this dissertation, the following conclusions can be made:

- The majority of pediatric trials published in 2007 were at high risk of bias, corresponding with a trend toward increased effect sizes. In spite of a movement towards improving methodological quality and requirements for trial registration, the majority of trials have not met these recommendations.
- Among a sample of pediatric trialists, we found that bias is a recognized concern; however they may lack the knowledge, willingness, or resources to properly address it. The major barriers to minimizing risk of bias in trials were related to awareness (e.g., insufficient formal training in research methods) and environment (e.g., negative attitudes towards research at individual and institutional levels). Positive relationships that support research interests were identified as a key facilitator.
- The use of social media in health care education and practice is growing, and there is a significant body of literature examining its uses. Currently, studies are primarily descriptive and focused on the use of social media in education, with communication as the most common purpose. The use of social media across disciplines and specialties, and for multiple purposes, suggests that social media tools and platforms may have widespread applicability and utility.
- Based on the above findings, we developed a wiki to be used as an educational tool to increase awareness and understanding of risk of bias among pediatric trialists. In our pilot test, participants found the risk of bias wiki straightforward and easy to use, providing suggestions to improve clarity and esthetics. The interactive format

was enticing to users and the components that allowed participation or emphasized practical applications over theory were preferred.

7.2. Recommendations

To continue efforts to improve the quality of pediatric randomized controlled trials, future directions include:

- Evaluating the effectiveness of the wiki as a learning tool for research methodology. Opportunities to investigate its use in workshops and in the classroom should be explored, including seeking informal feedback from users and designing formal studies, for example, using a controlled before-after design to determine whether the tool is beneficial as an adjunct to standard instruction.
- Investigating potential collaborations with gatekeepers in the research process to emphasize the value of rigorous design and conduct. The work that has been done relating to risk of bias, combined with the research and recommendations that have been compiled to address other important aspects of child health research under the umbrella of StaR Child Health provide a strong foundation for guidelines on designing and conducting trials in this population. Endorsing these guidelines would be advantageous to ethics review boards, funders, and journal editors.
- Increasing the availability of training opportunities in research methodology, and positioning these skills as an important and expected component of clinical practice. By making learning resources such as the risk of bias wiki available through research networks (e.g., StaR Child Health, Maternal Infant Child and Youth Research Network) and clinician-scientist training programs (e.g., Canadian Child Health Clinician Scientist Program), a new generation of trialists will be provided with a solid foundation in clinical research methodology.

7.3. Concluding statement

Future research in improving the methodology of child health trials will be dependent on positioning this work as a valuable component in providing optimal health care. Knowledge translation efforts can continue to focus on targeted messages, including the importance of minimizing the risk of bias of a study, and can also be extended to increase awareness of the value of well-conducted research in improving health outcomes. The use of the wiki can be further explored as one component of a strategy to address this research agenda.

Appendices

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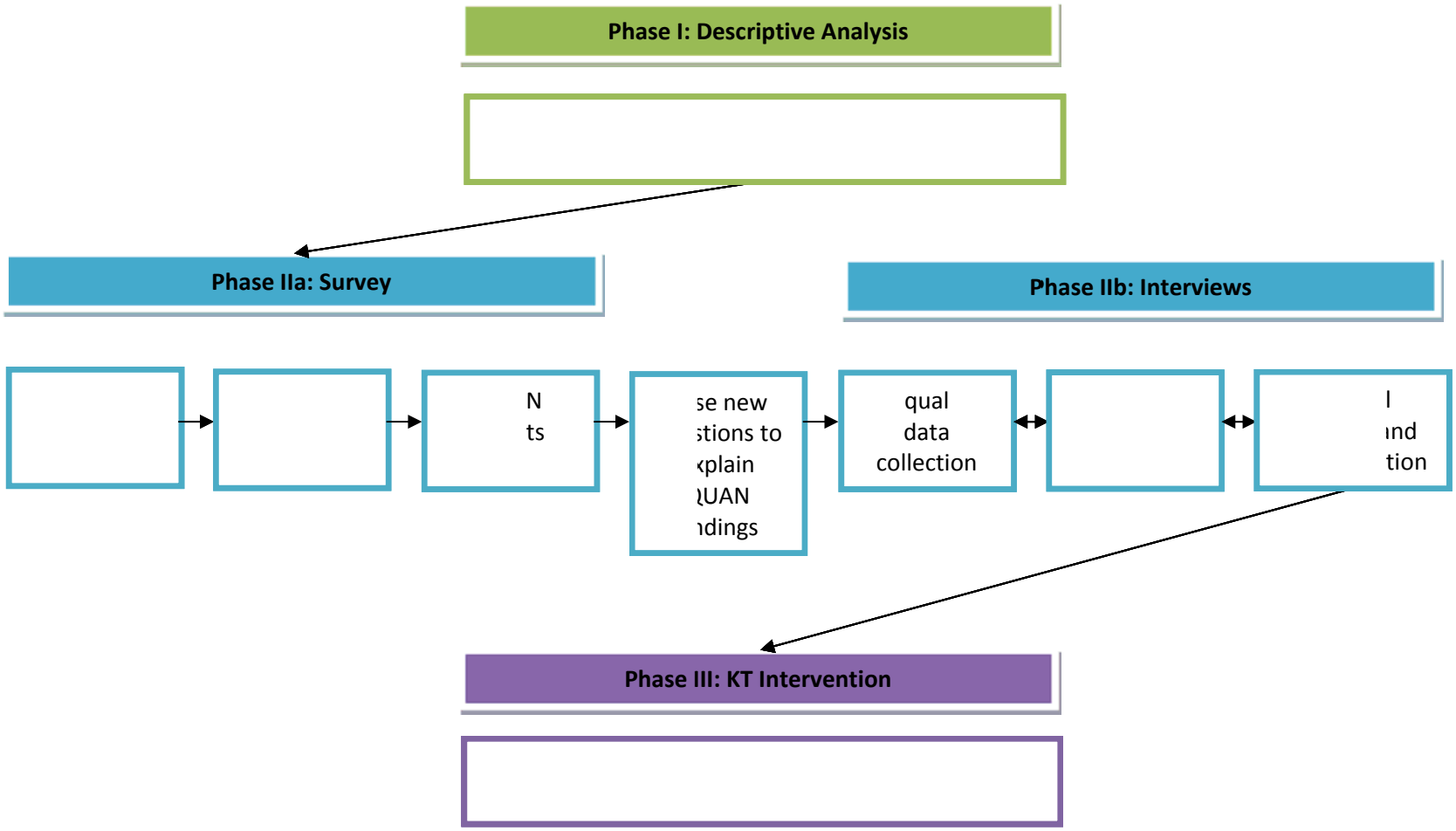
Chapter 6: Discussion

Appendix A. Illustration of mixed methods study design



RCT: randomized controlled trial; QUAN: quantitative, qual: qualitative (capitalization of QUAN indicates emphasis within an explanatory mixed methods design); KT: knowledge translation

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Appendix C. Search strategy

Cochrane Central (OVID)
Searched October 7, 2009

#1	(Infant* OR infancy OR Newborn* OR Baby* OR Babies OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child* OR Schoolchild* OR School age* OR Preschool* OR Kid or kids OR Toddler* OR Teen* OR Boy* OR Girl* OR Minors* OR Pubert* OR Pubescen* OR Prepubescen* OR Pediatric* OR Paediatric* OR Peadiatric* OR Nursery school* OR Kindergar* OR Primary school* OR Secondary school* OR Elementary school* OR High school* OR Highschool*):ti,ab,kw or (Adolesc*):ti,ab or (Infant OR Child OR Minors OR Puberty OR Pediatrics OR Schools):kw in Clinical Trials
#2	adolescent*:kw in Clinical Trials
#3	(adolescent* and (adult* or elderly or "middle aged" or "aged, 80 and over")):kw in Clinical Trials
#4	(#3 AND NOT #1)
#5	(#1 OR #2)
#6	(#5 AND NOT #4)

Appendix D. Children in trials 2007 - data extraction guide

Field	Response	Comments
Publication characteristics		
Please enter the following publication characteristics: Publication title: Publication year: Full journal title: First author: Country of corresponding author: Volume ID: Issue ID: Number of authors: Pages: Was there a working group? Type of journal: Language of publication:	 □Yes □No □General medical journal □Specialty medical journal □General pediatric journal □Specialty pediatric journal □Other	
Trial characteristics		
What is the study design?	□RCT parallel □RCT crossover □RCT factorial □Other (specify):	RCT **parallel**: A trial that compares two groups of people concurrently, one of which receives the intervention of interest and one of which is a control group. Some parallel trials have more than two comparison groups and some compare different interventions without including a non-intervention control group. (Also called independent group design**.**) RCT **crossover**: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the

		course of one treatment, are switched to another. For example, for a comparison of treatments A and B, the participants are randomly allocated to receive them in either the order A, B or the order B, A. Particularly appropriate for study of treatment options for relatively stable health problems. The time during which the first intervention is taken is known as the first period, with the second intervention being taken during the second period. RCT **factorial**: A trial design used to assess the individual contribution of treatments given in combination, as well as any interactive effect they may have. Most trials only consider a single factor, where an intervention is compared with one or more alternatives, or a placebo. In a trial using a 2x2 factorial design, participants are allocated to one of four possible combinations. For example in a 2x2 factorial RCT of nicotine replacement and counselling, participants would be allocated to: nicotine replacement alone, counselling alone, both, or neither. In this way it is possible to test the independent effect of each intervention on smoking cessation and the combined effect of (interaction between) the two interventions. This type of study is usually carried out in circumstances where no interaction is likely.
Based on the study hypothesis/objectives, which study type is described?	□Efficacy/Superiority □Equivalence □Non-inferiority □Not declared □None of the above □Unclear	**Efficacy/Superiority**: A study in which the authors intended to demonstrate a significant difference between treatments. **Equivalence**: A study in which the authors intended to show that there was no significant difference between treatments. **Non-inferiority**: A study in which the authors intended to show that the new treatment effect is not worse than the standard treatment effect.
In your opinion, what study type is consistent with the methods described?	□Efficacy/Superiority □Equivalence □Non-inferiority □None of the above □Unclear	
What is the unit of randomization?	□Individual	

	□Cluster	
What is the nature of the intervention?	□Drug □Vaccine □Natural health product □Device □Other	**Natural health products** include: -Vitamins and minerals -Herbal remedies -Homeopathic medicines -Traditional medicines such as traditional Chinese medicines -Probiotics, and -Other products like amino acids and essential fatty acids. (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php) A **device** is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: -recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, -intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or -intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." (http://www.fda.gov/CDRH/DEVADVICE/312.html)
What intervention(s) are tested?		
Is the study placebo controlled?	□Yes □No	
How many arms does the study have?		
Is the study multicentre?	□Yes □No □Unclear	
If yes, how many study sites are involved?		
Is the study multinational?	□Yes □No	
What is the sample size?		Target and enrolled sample size.

Is a sample size calculation reported?	□Yes □No	
Is the presence of subgroups (e.g. infants, preschoolers, school-aged, adolescents) reported?	□Yes □No	
Is a target age range described (e.g. in the inclusion criteria or baseline characteristics)?	□Yes □No	
What is the described age group (e.g. range, mean, median)?		Include any numerical values given.
How was the study population selected?	□Inpatients □Outpatients □Combined inpatients and outpatients □Doctors' office □Community □Unclear	
Is the method of obtaining consent described?	□Yes □No	
If yes, how was consent provided in the study?	□Parental permission □Parental permission and participant assent □Consent of a mature minor □N/A	
What diagnostic category(ies) are involved in the study?	□ Acute Respiratory Infections □ Airways □ Anaesthesia □ Back □ Bone, Joint and Muscle Trauma □ Childhood Cancer □ Consumers and Communication □ Cystic Fibrosis and Genetic Disorders □ Depression, Anxiety and Neurosis	Include the primary and secondary (if applicable) diagnostic categories.

	□ Developmental, Psychosocial and Learning □ Drugs and Alcohol □ Ear, Nose and Throat Disorders □ Effective Practice and Organisation of Care □ Epilepsy □ Eyes and Vision □ HIV/AIDS □ Haematological Malignancies □ Heart □ Hepato-Biliary □ Infectious Diseases □ Inflammatory Bowel Disease and Functional Bowel Disorders □ Injuries □ Menstrual Disorders and Subfertility □ Metabolic and Endocrine Disorders □ Movement Disorders □ Multiple Sclerosis □ Musculoskeletal □ Neonatal □ Neuromuscular Disease □ Oral Health □ Pain, Palliative and Supportive Care □ Peripheral Vascular Diseases □ Public Health □ Renal □ Schizophrenia	

	□ Sexually Transmitted Diseases □ Skin □ Tobacco Addiction □ Upper Gastrointestinal and Pancreatic Diseases □ Wounds □ Other □ N/A	
Is the presence of a Data Monitoring and Safety Committee reported?	□Yes □No □Unclear	
Did the DMSC examine data from adverse events?	□Yes □No □Unclear □Not Applicable	
Are stopping rules reported?	□Yes □No □Unclear	
Was the trial stopped early for benefit?	□Yes □No □Unclear	
What was the length of the follow-up period from the point of randomization?		
Were interim analyses planned?	□Yes □No □Unclear	
Did the trial proceed as planned?	□Yes □No □Unclear	
Is the funding source specified?	□Yes □No	
If yes, was industry funding declared?	□Yes □No	

	□N/A	
Outcomes and conclusions		
Is the primary outcome explicitly reported?	□Yes □No	
Can the primary outcome be inferred?	□Yes □No	Can be inferred from objectives/hypothesis if not explicitly stated. To select primary outcome, if necessary: 1. Choose the objective over the subjective outcome (*keep safety separate – not a primary outcome). 2. If the sample size calculation is based on an outcome, use it as the primary outcome. 3. If 1 and 2 aren't met, use the first outcome listed in the Results section as the primary outcome.
Which category best describes the type of primary outcome measured?	□Behavioural □Biomarker □Pain □Physiological □Psychological □Techniques/training □Quality of life □Other (specify): □N/A	**Behavioural:** e.g. attitudes, eating behaviours **Biomarker:** NIH definition: A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. E.g. blood glucose, urine cultures. **Pain:** e.g. pain relief, pain prevention **Physiological:** adapted from NIH definition: A characteristic or variable that reflects how a patient feels, functions, or survives. E.g. disease progression, mortality **Psychological:** e.g. depression assessment scores, neuropsychological test performance **Techniques/training:** method of intubation, effectiveness of a focus group **Quality of life:** e.g. SF-36, patient satisfaction
Is the justification for the choice of outcome described in the publication?	□Yes □No □Unclear	
Is the outcome measurement tool used valid?	□Yes □No □Unclear	
Is the primary outcome:	□Objective □Subjective	**Objective** outcomes include all cause mortality, measures based on a recognized laboratory procedure, surgical or instrumental

		outcomes and other objective measures. **Subjective** outcomes include patient reported outcomes, physician assessed disease outcomes, measures combined from several outcomes, and withdrawals or study dropouts. (Wood *et al.* BMJ 2008;336:601-605.)
Is the study described as a pilot or exploratory study?	□Yes □No	
Is there at least one outcome that is statistically significant?	□Yes □No	
If significant, which intervention is favoured?	□Treatment □Control □N/A	
Is a method for reporting adverse effects stated?	□Yes □No	
Are any adverse effects reported?	□Yes □No	
Was mortality included as an outcome?	□Yes □No □Unclear □Adverse event	
What are the authors' overall conclusions?	□Positive □Negative □Unclear	Based on the authors' personal conclusions, rather than statistical significance.
What is the effect estimate of the primary outcome?		If the outcome is measured at multiple time points, record one set of measurements: 1. follow the authors' intent if possible (e.g. clinically relevant; time point emphasized by the authors) 2. if unable to determine, pull for clinician judgement
Methodological quality		
Is the study described as intention to treat?	□Yes □No	
Is the method of blinding described?	□Yes □No	If the authors state that there is no blinding, check 'Yes', since it is described, and check 'No blinding' for the following question.

Who is blinded in the study (check all that apply)?	□Participants □Care providers □Outcome assessors □Analysts □Parents □No blinding □Unclear	
Registration and protocol characteristics		
In the publication, is registration of the trial declared?	□Yes □No	
Is the trial registered with a clinical trial registry?	□Yes □No	
If yes, which registry is used?		
Are the primary outcomes specified in the trial registry?	□Yes □No	
If specified, what primary outcomes are reported in the trial registry?		
Is a study protocol available from the corresponding author/study contact?	□Yes □No □No response	All of the authors will be emailed about their protocols, and this question can be answered pending their response.
If the protocol is not available, is the trial register sufficiently detailed to use as a protocol?	□Yes □No □N/A	A sufficiently detailed protocol will include explicitly stated primary outcomes.
Is the primary outcome stated in the protocol the same as in the publication?	□Yes □No □N/A	Use N/A if protocol is unavailable.
Has the primary outcome stated in the protocol been made a secondary outcome in the publication?	□Yes □No □N/A	Use N/A if protocol is unavailable.
Is the primary outcome stated in the protocol omitted from the publication?	□Yes □No □N/A	Use N/A if protocol is unavailable.
Was a non primary outcome in the protocol	□Yes	Use N/A if protocol is unavailable.

changed to primary in the publication?	□No □N/A	
Is an outcome that was not included in the protocol a primary outcome in the publication?	□Yes □No □N/A	Use N/A if protocol is unavailable.
Were interim analyses planned?	□Yes □No □Unclear	
Did the trial proceed as planned?	□Yes □No □Unclear	
If not, what was the reason?	□Futility □Efficacy □Harm □Recruitment issues □Changes in protocol □Other □Not applicable	
If other, please specify:		

Appendix E. Risk of bias assessment guidelines

*Use these decision rules in addition to the guidelines outlined in the Cochrane criteria.

Sequence generation:

- If blocked randomization, permutation, or stratification is specified, assume the randomization sequence was computer-generated and answer YES.
- If the description only includes 'random', 'randomly generated', 'randomized', etc, do not assume additional details and answer UNCLEAR.

Allocation concealment:

- If the randomization is conducted by central telephone, pharmacy, etc, assume this is adequate and answer YES.

Blinding:

- Determine whether the blinding is likely to be broken, and whether the outcomes in unblinded studies are likely to be influenced by the lack of blinding.
- If a study is described as "double-dummy", assume that this is appropriate and answer YES. If it is described as "double-blind" without further details, answer UNCLEAR.

Incomplete outcome data:

- Look for intention-to-treat analysis. If this was done appropriately, answer YES.
- If all participants were accounted for (i.e. no drop-outs or censored analysis conducted), answer YES.
- If the numbers and reasons for withdrawal/drop-outs were described and comparable across groups (and ≤ approximately 10%), answer YES.
- If there is greater than 10% drop-out, consider UNCLEAR or NO.

Selective outcome reporting:

- If the study protocol is available, compare the outcomes reported in the publication to those specified in the protocol. Answer YES if the outcomes in the two documents match.
- If the study protocol is not available, compare the outcomes reported in the Methods and Results sections. Answer YES if these match.

"Other" sources of bias:

- Assess for baseline imbalances that could have biased the results (or were not accounted for).
- Assess for early stopping for benefit.

- Assess for appropriateness of cross-over design (e.g. inadequate wash-out period).
- Assess for inappropriate influence of funders that could have biased the results.
    - If sponsor is acknowledged and there is a clear statement regarding no involvement of sponsor in trial conduct or data management/analysis, answer YES.
    - If sponsor is acknowledged and no one from the sponsoring agency was an author, answer YES.
    - If sponsor is acknowledged and someone from the sponsoring agency was an author, answer NO.
    - If a drug/intervention is provided by industry, but the trial has no other inappropriate influence of funding, answer YES.
    - If there is no mention of funding source, answer UNCLEAR.
- Note any “other” sources of bias.

Appendix F. Author survey

*Skip logic was included to automatically bypass irrelevant questions (e.g. a response of "no" for #1 would skip #2-4).

1. Was your study registered with a public trial registry?
- Yes
- No

2. Where is your trial registered (select all that apply)?
- Australian New Zealand Clinical Trials Registry (ANZCTR)
- Chinese Clinical Trial Register
- ClinicalTrials.gov
- Clinical Trials Registry - India
- Current Controlled Trials (ISRCTN Register)
- German Clinical Trials Register
- Iranian Registry of Clinical Trials
- Sri Lanka Clinical Trials Registry
- The Netherlands National Trial Register
- Other (please specify)

3. When was your trial registered?
- Before patient recruitment
- During patient recruitment
- After patient recruitment

4. What were your reasons for registering your trial (select all that apply)?
- I believe that trials should be registered as a means of full public disclosure
- I endorse the statement regarding public trial registration made by the International Committee of Medical Journal Editors
- Trial registration is necessary for publication in some peer-reviewed journals
- Trial registration was required by the funding agency
- Trial registration was required by the Research Ethics Board
- Other (please specify)

5. What were your reasons for not registering your trial (select all that apply)?
- Lack of time
- Lack of resources
- I was not familiar with the process for trial registration
- Cost associated with registration
- I don't see a benefit to trial registration
- Trial was initiated prior to registration endorsement by the International Committee of Medical Journal Editors
- Other (please specify)

6. Did you prepare a formal, written, study protocol prior to implementing your trial?
- Yes
- No

7. Is your protocol publicly available (e.g. on a publicly available website, published in a journal)?
- Yes
- No
- If yes, where is it located?

8. If your protocol is not publicly available, would you be willing to share it with us? All information will be kept confidential, will only be used for the purposes of this study, and will be reported on in aggregate form.
- No
- Yes (please send to study coordinator as per the contact information in the cover letter)
- Yes, I would be willing to share it but I cannot locate it
- Other (please specify)

9. Did the study conduct differ from that specified in the protocol?
- Yes
- No

10. How would you rate the difference in study conduct from that indicated in the protocol?
- Major difference
- Minor difference

11. How did the study conduct differ from that specified in the protocol (select all that apply)?
- Recruitment of participants
- Sample size
- Intervention in the treatment arm
- Intervention in the control arm
- Outcome measurement
- Monitoring of safety and efficacy data
- Duration of study
- Length of follow-up
- Analysis
- Other (please specify)

12. What was the primary outcome measure(s) in your study?

13. When was the primary outcome specified?
- In the protocol before the trial began

- In the protocol during the trial
- During data analysis
- Following data analysis
- Other (please specify)

14. Please list any outcomes that were measured in the trial, but were not reported in the publication. Please exclude baseline characteristics and data collected for administrative purposes.

15. For each outcome listed in Question 14, indicate whether or not the result was statistically significant ($p \leq 0.05$).

16. For each outcome listed in Question 14, indicate whether it was a primary, secondary, or unspecified outcome in the protocol.

17. For each outcome listed in Question 14, indicate whether it was of little, moderate, or high clinical importance.

18. What were your reasons for not reporting the above outcomes (select all that apply)?
- Journal imposed space limit
- Authors' concern about space
- Not statistically significant
- Not clinically important
- Not intended for inter-group comparisons
- Other (please specify)

19. Were outcomes measured at any timepoints that were not reported on?
- Yes
- No
- If yes, please specify

20. Which study type is consistent with your trial?
- Efficacy/superiority
- Equivalence
- Non-inferiority
- None of the above (please specify)

21. Would you consider the results of your trial to be:
- Positive
- Negative
- Null
- Unclear

22. Did you conduct sample size calculations before the study began?
- Yes

- No

23. If yes, which outcome(s) was the sample size calculation based on?

24. Prior to the publication of your trial, was your manuscript ever refused by a journal because the trial hadn't been registered?
- Yes
- No
- Not Applicable

25. Which most closely describes your academic rank when the trial was initiated?
- Research Assistant
- Research Associate
- Lecturer
- Assistant Professor
- Associate Professor
- Full Professor
- Other (please specify)

26. How many trials (RCTs) had you previously completed at the time that this trial was initiated?

27. What is your gender?
- Female
- Male

28. What was your age at the time that this trial was initiated?
- Less than 30 years
- 30 - 39 years
- 40 - 49 years
- 50 - 59 years
- 60 years or more

Appendix G. Odds ratios for risk of bias by selected variables

Table G1. High Risk of Bias by Sequence Generation (N=300)

Variable		Sequence Generation OR (95%CI)	*p*-value
Trial registration		0·44 (0·25,0·76)	<0·01
Industry funding		1·24 (0·68,2·25)	0·48
Multi-centre trial		1·24 (0·77,2·02)	0·38
Type of journal			
	Specialty medical	Reference	
	General medical	1·36 (0·52,3·55)	0·53
	Specialty pediatric	1·11 (0·63,1·94)	0·72
	General pediatric	0·79 (0·41,1·53)	0·49
Nature of intervention			
	Drug	Reference	
	Device	1·03 (0·52,2·07)	0·92
	Natural health product	0·78 (0·33,1·85)	0·57
	Vaccine	1·60 (0·56,4·56)	0·38
	Other	2·06 (1·18,3·57)	0·01
Outcome category			
	Physiological	Reference	
	Behavioural	1·46 (0·71,3·01)	0·30
	Biomarker	1·53 (0·75,3·15)	0·24
	Pain	0·96 (0·38,2·43)	0·93
	Psychological	1·56 (0·52,4·69)	0·43
	Quality of life	8·17 (0·42,160·72)	0·17
	Techniques/Training	0·78 (0·21,2·86)	0·71
	Other	2·63 (0·78,8·88)	0·12

Table G2. High Risk of Bias by Allocation Concealment (N=300)

Variable		Allocation Concealment OR (95%CI)	*p*-value
Trial registration		0.31 (0·18,0·56)	<0·01
Industry funding		1·17 (0·61,2·25)	0·63
Multi-centre trial		1·34 (0·76,2·37)	0·31
Type of journal			
	Specialty medical	Reference	
	General medical	0·58 (0·21,1·65)	0·31
	Specialty pediatric	0·84 (0·43,1·63)	0·60
	General pediatric	0·49 (0·24,1·00)	0·05
Nature of intervention			
	Drug	Reference	
	Device	1·56 (0·70,3·47)	0·28
	Natural health product	0·86 (0·35,2·12)	0·75
	Vaccine	1·37 (0·42,4·54)	0·60
	Other	2·58 (1·30,5·13)	<0·01
Outcome category			
	Physiological	Reference	
	Behavioural	1·84 (0·72,4·73)	0·20
	Biomarker	1·34 (0·57,3·14)	0·51
	Pain	0·55 (0·21,1·44)	0·23
	Psychological	1·35 (0·36,5·07)	0·65
	Quality of life	0·74 (0·07,8·33)	0·81
	Techniques/Training	1·48 (0·30,7·21)	0·63
	Other	2·03 (0·43,9·51)	0·37

Table G3. High Risk of Bias by Blinding (N=300)

Variable		Blinding OR (95%CI)	*p*-value
Trial registration		0·45 (0·26,0·79)	0·01
Industry funding		0·41 (0·22,0·76)	<0·01
Multi-centre trial		1·16 (0·72,1·88)	0·54
Type of journal			
	Specialty medical	Reference	
	General medical	1·27 (0·49,3·29)	0·62
	Specialty pediatric	1·62 (0·92,2·84)	0·10
	General pediatric	0·91 (0·47,1·77)	0·79
Nature of intervention			
	Drug	Reference	
	Device	3·37 (1·62,7·02)	<0·01
	Natural health product	0·70 (0·28,1·74)	0·70
	Vaccine	0·36 (0·10,1·34)	0·13
	Other	3·00 (1·71,5·27)	<0·01
Outcome category			
	Physiological	Reference	
	Behavioural	1·85 (0·89,3·83)	0·10
	Biomarker	1·55 (0·76,3·17)	0·23
	Pain	1·98 (0·77,5·09)	0·16
	Psychological	0·99 (0·33,2·98)	0·99
	Quality of life	0·66 (0·06,7·42)	0·74
	Techniques/Training	5·28 (1·09,25·61)	0·04
	Other	2·97 (0·88,10·03)	0·08

Table G4. High Risk of Bias by Incomplete Data (N=300)

Variable		Incomplete Data OR (95%CI)	*p*-value
Trial registration		0·46 (0·25,0·84)	0·01
Industry funding		0·82 (0·43,1·56)	0·55
Multi-centre trial		1·12 (0·68,1·85)	0·65
Type of journal			
	Specialty medical	Reference	
	General medical	0·95 (0·34,2·63)	0·92
	Specialty pediatric	1·63 (0·92,2·90)	0·09
	General pediatric	0·91 (0·47,1·77)	0·09
Nature of intervention			
	Drug	Reference	
	Device	2·56 (1·26,5·21)	0·01
	Natural health product	2·99 (1·25,7·10)	0·01
	Vaccine	0·59 (0·16,2·20)	0·43
	Other	1·93 (1·09,3·42)	0·02
Outcome category			
	Physiological	Reference	
	Behavioural	2·10 (1·01,4·35)	0·05
	Biomarker	1·02 (0·48,2·15)	0·96
	Pain	1·25 (0·48,3·24)	0·64
	Psychological	0·51 (0·14,1·91)	0·32
	Quality of life	3·76 (0·33,42·33)	0·28
	Techniques/Training	1·88 (0·52,6·76)	0·33
	Other	1·17 (0·37,3·75)	0·79

Table G5. High Risk of Bias by Selective Outcome Reporting (N=300)

Variable		Selective Outcome Reporting OR (95%CI)	*p*-value
Trial registration		3·23 (1·72,6·04)	<0·01
Industry funding		1·36 (0·64,2·91)	0·43
Multi-centre trial		1·24 (0·67,2·30)	0·49
Type of journal			
	Specialty medical	Reference	
	General medical	1·83 (0·61,5·49)	0·28
	Specialty pediatric	0·95 (0·44,2·05)	0·90
	General pediatric	1·46 (0·65,3·30)	0·36
Nature of intervention			
	Drug	Reference	
	Device	0·37 (0·12,1·11)	0·08
	Natural health product	1·10 (0·40,3·01)	0·86
	Vaccine	0·24 (0·03,1·93)	0·18
	Other	0·82 (0·41,1·62)	0·56
Outcome category			
	Physiological	Reference	
	Behavioural	1·10 (0·44,2·75)	0·83
	Biomarker	0·88 (0·34,2·31)	0·80
	Pain	1·14 (0·36,3·66)	0·82
	Psychological	0·76 (0·16,3·58)	0·73
	Quality of life	9·13 (0·80,104·03)	0·07
	Techniques/Training	0·21 (0·01,3·76)	0·29
	Other	1·37 (0·36,5·28)	0·65

Table G6. High Risk of Bias by "Other" Sources of Bias (N=300)

Variable		"Other" Sources of Bias OR (95%CI)	*p*-value
Trial registration		0·47 (0·27,0·81)	0·01
Industry funding		4·72 (2·46,9·07)	<0·01
Multi-centre trial		1·28 (0·77,2·13)	0·34
Type of journal			
	Specialty medical	Reference	
	General medical	0·60 (0·23,1·57)	0·30
	Specialty pediatric	1·45 (0·79,2·69)	0·23
	General pediatric	0·74 (0·38,1·45)	0·38
Nature of intervention			
	Drug	Reference	
	Device	0·82 (0·39,1·71)	0·59
	Natural health product	0·68 (0·28,1·64)	0·39
	Vaccine	2·96 (0·64,13·72)	0·16
	Other	0·49 (0·28,0·87)	0·01
Outcome category			
	Physiological	Reference	
	Behavioural	0·90 (0·43,1·90)	0·79
	Biomarker	1·36 (0·63,2·94)	0·43
	Pain	1·73 (0·60,4·98)	0·31
	Psychological	0·77 (0·25,2·32)	0·64
	Quality of life	1·15 (0·10,12·96)	0·91
	Techniques/Training	1·34 (0·33,5·38)	0·68
	Other	0·92 (0·29,2·94)	0·89

Table G7. High Risk of Bias by Overall Risk of Bias (N=300)

Variable		Overall Risk of Bias OR (95%CI)	*p*-value
Trial registration		0·29 (0·12,0·69)	0·01
Industry funding		1·28 (0·50,3·29)	0·61
Multi-centre trial		2·10 (0·75,5·87)	0·16
Type of journal			
	Specialty medical	Reference	
	General medical	0·49 (0·13,1·91)	0·31
	Specialty pediatric	3·15 (0·70,14·26)	0·14
	General pediatric	0·95 (0·30,3·04)	0·93
Nature of intervention			
	Drug	Reference	
	Device	1·65 (0·45,6·07)	0·45
	Natural health product	0·66 (0·20,2·22)	0·50
	Vaccine	1·81 (0·22,14·81)	0·58
	Other	5·48 (1·20,24·91)	0·03
Outcome category			
	Physiological	Reference	
	Behavioural	3·20 (0·41,25·17)	0·27
	Biomarker	0·75 (0·23,2·44)	0·64
	Pain	1·74 (0·22,13·97)	0·60
	Psychological	1·19 (0·14,9·78)	0·87
	Quality of life	0·66 (0·03,13·44)	0·79
	Techniques/Training	1·98 (0·11,35·61)	0·64
	Other	0·50 (0·10,2·50)	0·40

Appendix H. Search strategy

Cochrane Central (OVID)

Searched February 9, 2010

Notes: Limited search results to 2008, 2009

1. exp canada/ 2. canada.cp. 3. (canada or canadian$ or alberta or british columbia or columbie britannique).af. 4. (saskatchewan or manitoba or ontario or quebec or new brunswick or nouveau brunswick).af. 5. (nova scotia or nouvelle ecosse or prince edward island or ile du prince edward or newfoundland or terre neuve or labrador or nun?v?t or nun?v?t or nwt or territoires du nord ouest or northwest territories or yukon).af. 6. (canada or canadian$ or alberta or british columbia or columbie britannique).in. 7. (saskatchewan or manitoba or ontario or quebec or new brunswick or nouveau brunswick).in. 8. (nova scotia or nouvelle ecosse or prince edward island or ile du prince edward or newfoundland or labrador or nun?v?t or nwt or northwest territories or territoires du nord ouest or yukon).in. 9. or/1-8 10. Pediatrics/ 11. Child/ 12. Adolescent/ 13. child*.tw. 14. adolescen*.tw. 15. p*ediatric*.tw. 16. or/10-15	17. randomized controlled trial.pt. 18. randomi?ed.ab. 19. placebo.ab. 20. drug therapy.fs. 21. randomly.ab. 22. trial.ab. 23. groups.ab. 24. controlled clinical trial.pt 25. or/17-24 26. 9 and 16 and 25 27. 9 and 16 28. limit 27 to randomized controlled trial 29. 26 or 28 30. limit 29 to yr="2008" 31. limit 29 to yr="2009"

Appendix I. Information sheets and consent forms

UNIVERSITY OF ALBERTA

Department of Pediatrics/ARCHE
Faculty of Medicine & Dentistry

Aberhart Centre One, 11402 University Avenue
Edmonton, Alberta, Canada T6G 2J3

www.ualberta.ca
www.ualberta.ca/ARCHE

Tel: (780) 492-1078
Fax: (780) 407-6435

September 15, 2010

Study Title: Barriers and Facilitators in Conducting Pediatric Randomized Controlled Trials

Student Investigator: Michele Hamm
Tel: 780.492.1241
Fax: 780.407.6435
Email: michele.hamm@ualberta.ca

Supervisor: Dr Terry P. Klassen
Tel: 204.789.3754
Fax: 204.789.3915
Email: tklassen@mich.ca

Dear Colleague,

I am a doctoral student in the Department of Pediatrics at the University of Alberta. As part of my dissertation I am writing to invite you to participate in a survey investigating the barriers and facilitators faced by researchers when conducting randomized controlled trials in child health.

Background: Randomized controlled trials (RCTs) are considered the gold standard for research on therapeutic interventions and provide excellent evidence for guiding decisions regarding clinical care. There is limited evidence available about the validity of pediatric trials. An issue of concern is that of bias. Bias is a systematic error that when introduced into a study can influence the estimation of effect size, obscuring the true effect of an intervention. Assessment of the risk of bias of a study can be used as an indicator of internal validity, and can be used as a gauge of the level of confidence that can be placed in the reported effects of an intervention.

We are interested in determining the factors that influence how pediatric trials are designed, conducted, and reported, and how this affects their internal validity.

Purpose: We are conducting a survey of researchers who were involved in pediatric trials published in 2008 and 2009, and you have been included in our sample.

Procedures: We would appreciate it if you would complete this brief questionnaire in reference to your experience as a trialist. The survey has been pilot tested and it should only take about 15 minutes of your time. To access the survey, please follow the link:

https://www.surveymonkey.com/s/HV2TG9W

Possible Benefits and Harms: The possible benefits to you for participating in this study are that you would be contributing to new knowledge about the methodology surrounding trials in children, potentially leading to higher quality research in pediatrics. We anticipate minimal or no risk of harm from the research study.

Confidentiality and Data Security: All survey responses will be encrypted and kept anonymous, and all other information collected from or about you will be kept confidential and will be reported in aggregate form. The principal investigator will be responsible for storing the

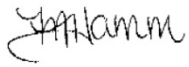
data. It will be stored in the Department of Pediatrics at the University of Alberta for a period of five years.

Voluntary Participation: You are free to decline participation or withdraw from the study at any time with no adverse consequences to you. If the study is not undertaken or if it is discontinued at any time, there will be no adverse consequences to you. None of the investigators will be aware of your decision on participation since you will be identified by number and not by name. By submitting the survey your consent to participate is implied.

If you would prefer to complete a paper copy of the survey, or if you have any questions or concerns, please contact me at michele.hamm@ualberta.ca or at 780.492.1241, or my supervisor, Dr Terry Klassen, at tklassen@mich.ca or at 204.789.3754. If you have any questions regarding your rights as a research participant, please contact the Health Research Ethics Board at 780.492.0302. Collect calls are accepted.

Thank you for your consideration.

Sincerely,



Michele Hamm, MSc

Department of Pediatrics
8414 Aberhart Centre
University of Alberta
Edmonton, Alberta, Canada

Tel: 780.492.1241
Fax: 780.407.6435
Email: michele.hamm@ualberta.ca

UNIVERSITY OF ALBERTA
Department of Pediatrics/ARCHE
Faculty of Medicine & Dentistry
Aberhart Centre One, 11402 University Avenue
Edmonton, Alberta, Canada T6G 2J3
www.ualberta.ca
www.ualberta.ca/ARCHE
Tel: (780) 492-1078
Fax: (780) 407-6435

Study Title: Barriers and Facilitators in Conducting Pediatric Randomized Controlled Trials

Principal Investigator: Dr Terry P. Klassen
Tel: 204.789.3754
Email: terry.klassen@ualberta.ca

Student Investigator: Michele Hamm
Tel: 780.492.1241
Email: michele.hamm@ualberta.ca

What is the study about? The purpose of this study is to investigate the barriers and facilitators faced by researchers when conducting randomized controlled trials in child health. We are interested in determining the factors that influence how pediatric trials are designed, conducted, and reported, and how this affects their internal validity. We hope to use this information to develop a knowledge translation strategy to help pediatric researchers minimize risk of bias in future trials. The telephone interview will be about some or all of the following:

- Your beliefs, behaviours, and attitudes about conducting research on children
- Your perceptions of the barriers and facilitators related to appropriate trial design and conduct in pediatrics
- Your thoughts on the utility of potential intervention strategies to minimize risk of bias.

The telephone interview will take about 30 to 60 minutes and will occur at a convenient time. It will be taped in order to help the researchers interpret the information accurately. You may refuse to answer any questions, stop the interview at any time, or withdraw from the study. You can decline to discuss any topic in the interview if you wish.

Possible Benefits and Harms: The possible benefits to you for participating in this study are that you would be contributing to new knowledge about the methodology surrounding trials in children, potentially leading to higher quality research in pediatrics. We anticipate minimal or no risk of harm from the research study.

Your Privacy: All information will be held confidential (or private). The information that you provide will be kept in a secure area (i.e., locked filing cabinet). Your name or any other information identifying you will not be attached to the information you gave. Your name will also never be used in any presentations or publications of the study results. The data gathered from this study will be aggregated so as not to identify any person. Direct quotations may be used in the publications, however the quotations will be presented in a manner that removes any identifiable information. The information gathered for this study may be looked at again in the future to help us answer other study questions. If so, the ethics review board will first review the study to ensure the information is used ethically.

Questions: If you have questions or concerns about this study at any time, you may contact Michele Hamm at 780.492.1241 or michele.hamm@ualberta.ca.

Concerns: Please contact the Health Research Ethics Board at 780.492.0302 should you have any questions regarding your rights as a participant in a research study.

Part 1 (to be completed by the Principal Investigator):

Title of Project: Barriers and Facilitators in Conducting Pediatric Randomized Controlled Trials

Principal Investigator(s):	Phone Number(s):
Dr. Terry Klassen	204.789.3754
Student Investigator:	Phone Number(s):
Michele Hamm	780.492.1241

Part 2 (to be completed by the research subject):

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the study Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your responses?	☐	☐

Who explained this study to you? _____

I agree to take part in this study: YES ☐ NO ☐

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

Appendix J. Survey of pediatric trialists

Individual-level factors

Item	Disagree n (%)	Neutral n (%)	Agree n (%)	Don't Know n (%)	Total n
Bias, or systematic error, is a problem in pediatric trials	29 (15.7)	24 (13.0)	**126 (68.1)**	6 (3.2)	185
In general, researchers consider a trial's potential for bias when they are making clinical recommendations based on the study's results	32 (17.5)	18 (9.8)	**124 (67.8)**	9 (4.9)	183
Any trial conducted is better than no trial at all	**130 (70.7)**	7 (3.8)	46 (25.0)	1 (0.5)	184
I am aware of published research on bias in randomized controlled trials	16 (10.1)	8 (5.1)	**132 (83.5)**	2 (1.3)	158
I keep up with published research on bias in randomized controlled trials	52 (33.1)	25 (15.9)	**79 (50.3)**	1 (0.6)	157
I am interested in staying current with literature describing and analyzing research methods	4 (2.5)	7 (4.5)	**146 (93.0)**	-	157
I find the volume of published literature on research methods overwhelming and have trouble keeping up with this literature	28 (17.8)	26 (16.6)	**99 (63.1)**	4 (2.5)	157
I think there is evidence that changes are needed to some aspects of how randomized controlled trials are conducted	7 (4.5)	31 (19.7)	**113 (72.0)**	6 (3.8)	157
I feel that research on bias is relevant to my work	2 (1.3)	5 (3.2)	**150 (95.5)**	-	157
I am receptive to new ideas that may lead to changes in how I conduct my research	-	1 (0.6)	**154 (98.7)**	1 (0.6)	156
Minimizing bias is an issue I am conscious of when conducting my research	2 (1.1)	5 (2.7)	**176 (95.7)**	1 (0.5)	184
I am confident in my ability to evaluate the quality of published trials	4 (2.6)	5 (3.2)	**145 (94.2)**	-	154
How confident are you in your understanding of what bias is?	**mean:** 5.4/7				
How likely is it that you will consider risk of bias in the next trial in which you are involved?	**mean:** 5.0/7				
How confident are you that you can minimize the risk of bias in your own research?	**mean:** 6.2/7				

Introduction of bias into a trial:	Disagree n (%)	Neutral n (%)	Agree n (%)	Don't Know n (%)	Total n
Sequence Generation					
Computer-generated randomization sequence	**141 (83.4)**	8 (4.7)	19 (11.2)	1 (0.6)	169
Group allocation according to an alternating sequence	48 (28.4)	14 (8.3)	**101 (59.8)**	6 (3.6)	169
Group allocation according to patient chart numbers	36 (21.7)	16 (9.6)	**108 (65.1)**	6 (3.6)	166

Group allocation by flipping a coin	**86 (51.2)**	25 (14.9)	55 (32.7)	2 (1.2)	168
Allocation Concealment					
Centralized group allocation (e.g., by the pharmacy or a call centre)	**88 (53.0)**	18 (10.8)	47 (28.3)	13 (7.8)	166
Blinding					
Absence of blinding in a study with objective outcomes (e.g., mortality)	49 (29.3)	11 (6.6)	**105 (62.9)**	2 (1.2)	167
Absence of blinding in a study with subjective outcomes (e.g., pain scale)	20 (12.5)	5 (3.1)	**133 (83.1)**	2 (1.3)	160
Selective Outcome Reporting					
Reporting limited to statistically significant outcomes	25 (15.0)	16 (9.6)	**123 (73.7)**	3 (1.8)	167
Reporting limited to clinically significant outcomes	30 (17.9)	17 (10.1)	**117 (69.6)**	4 (2.4)	168
Incomplete Outcome Reporting					
Per-protocol analyses (analyzing participants' results as treated, rather than according to original group assignments)	24 (14.8)	11 (6.8)	**121 (74.7)**	6 (3.7)	162
Intention-to-treat analyses (analyzing participants' results according to original group assignments, rather than as treated)	**102 (63.4)**	14 (8.7)	41 (25.5)	4 (2.5)	161
Modified intention-to-treat analyses (analyzing results for participants who have met a set of minimum requirements)	*58 (36.0)*	34 (21.1)	*58 (36.0)*	11 (6.8)	161
Other Sources of Bias					
Trial stopped early for benefit	40 (25.2)	23 (14.5)	**90 (56.6)**	6 (3.8)	159
Trial stopped early for harm	50 (31.3)	23 (14.4)	**81 (50.6)**	6 (3.8)	160
Full industry sponsorship	26 (16.3)	21 (13.1)	**109 (68.1)**	4 (2.5)	160
Partial industry sponsorship	32 (20.0)	25 (15.6)	**99 (61.9)**	4 (2.5)	160
Receipt of industry donations (e.g., study drugs)	48 (30.0)	28 (17.5)	**81 (50.6)**	3 (1.9)	160

Institution-level factors

Item	Disagree n (%)	Neutral n (%)	Agree n (%)	Don't Know n (%)	Total n
I find that applying methodologic research is often not practical in clinical trial settings	**89 (56.3)**	18 (11.4)	45 (28.5)	6 (3.8)	158
I feel that I have access to sufficient resources (e.g., staff) to conduct a high-quality trial	48 (30.4)	16 (10.4)	**90 (58.4)**	-	154
I find that institutional requirements align well with efforts to minimize bias in conducting trials	45 (29.2)	20 (13.0)	**82 (53.2)**	7 (4.5)	154
I find that the logistics of conducting a trial often make it difficult to minimize bias	52 (33.5)	19 (12.3)	**82 (52.9)**	2 (1.3)	155
My colleagues conduct research that is methodologically rigorous	12 (6.9)	26 (14.9)	**131 (75.3)**	5 (2.9)	174
I find it hard to report the details of my research as conducted because of space constraints in my target journals	61 (39.6)	17 (11.0)	**76 (49.4)**	-	154
I find it hard to publish my research without reporting statistically significant results	33 (21.6)	13 (8.5)	**102 (66.7)**	5 (3.3)	153
I have the authority to change how research is conducted within my research group	8 (5.1)	7 (4.5)	**142 (90.4)**	-	157
I find that lack of sufficient funding limits how well I am able to conduct my research	29 (18.7)	17 (11.0)	**109 (70.3)**	-	155
I find that rigorous methods (e.g., adhering to standards such as those set out in the CONSORT Statement) are encouraged by one or more of my colleagues and/or supervisors	9 (5.9)	16 (10.5)	**123 (80.4)**	5 (3.3)	153
I have opportunities to discuss research methods with knowledgeable colleagues	8 (5.3)	2 (1.3)	**141 (92.8)**	1 (0.7)	152

Appendix K: Sample interview guide

Thank you for agreeing to talk with me about your experience with bias in pediatric trials.

1. Tell me about your experience conducting trials with children.
   Probe:
   - How many trials conducted
   - Who designs the trials
   - Area/condition studied
   - Research experiences with the kids, parents, health care providers

2. Tell me about how considerations of bias are incorporated into your research.
   Probe:
   - Randomization
   - Allocation concealment
   - Blinding
   - Incomplete outcome data
   - Selective outcome reporting
   - "Other" (funding, cluster RCTs, etc.)

3. In our survey, we found that knowledge about issues related to bias, limits on reporting (e.g. space, reporting statistically significant findings), and some logistical issues were commonly identified as barriers to conducting methodologically rigorous trials. Can you tell me whether you have had a similar experience?
   a. Are there other factors that you would consider barriers? Describe.
   b. Have you been able to overcome these barriers? How?

4. Some of the common facilitators included having knowledgeable colleagues and the availability of tools like the CONSORT Statement. Have you found these to be helpful?
   a. Are there other factors that you would consider facilitators? Describe.
   b. How have these facilitators made it easier for you to conduct rigorous trials?

5. What challenges have you faced in conducting RCTs in pediatrics?
   a. Do your ideas about how trials should be conducted ever conflict with the reality of studying children? How?
   b. What level are the barriers at? (E.g. individual, group, etc.)

6. One potential intervention identified in the survey was an online resource centre. Do you think that would be useful?
   a. Have you used other online resources? Which ones?
   b. What would you like to see in such a tool?

7. Another intervention with some support was a checklist or reminder. Do you think that would be useful?
   a. Have you used other checklists? Which ones?
   b. What would you like to see in a checklist?

8. Are there other strategies that would be useful to you in minimizing bias in pediatric trials?
   Probe:
   - Educational materials?
   - Lectures or seminars?
   - Champion/opinion leaders?
   - Posters?
   - Other – please explain

Thank you for your thoughtful answers to my questions. Are there **any other comments** you would like to make that might help us understand bias in pediatric trials?

May we approach you again should we have any questions about what you have told us?

Appendix L. Interview codebook

CATEGORY	SYSTEM LEVEL	THEME	CODE	DEFINITION
SPECIFIC BIASES		**Internal validity:** *domains identified by the Cochrane Risk of Bias tool*	Allocation concealment	concealment of the allocation sequence from those involved in the enrolment and assignment of participants
			Blinding	concealment of the assigned treatment group from the patients, study personnel, and/or outcome assessors
			Incomplete outcome data	missing outcome data due to attrition during the study or exclusions from the analysis
			Other sources of bias	further concerns that may introduce threats to internal validity
			Randomization	assignment to treatment groups based on the use of a randomized sequence
		External validity: *generalizability of study findings to other populations and conditions*	Generalizability	applicability of study findings to other populations and conditions
BARRIERS	Personal	**Knowledge:** *lack of awareness of and/or familiarity with issues relevant to internal validity*	Awareness	knowledge and awareness of issues relevant to bias
			Interest	interest in seeking out methods to minimize risk of bias
			Priorities	differing stakeholder priorities: conflict between doing research to get an accurate answer and wanting to fast-track to using the best therapy for patients

		Science is the easy part	perception that scientific method is less of a barrier to good trials than more pragmatic issues
		Logistics (-ve)	factors that negatively impact the ability to attract or retain qualified research staff
		Equipoise	issues around true clinical uncertainty
		Formal training	addressing training in research methodology
Environmental	**Clinical care vs. clinical research:** *conflicts between the demands and priorities of the care and research paradigms*	Clinical care vs. clinical research	conflicts between the demands and priorities of the care and research paradigms
		Priorities	differing stakeholder priorities: balancing the needs of individuals and populations
		Protective	protective of the interests of the child
		Equipoise	issues around true clinical uncertainty
	Logistics: *challenges related to the planning, implementation, and coordination of the details of a trial*	Interest	conflict between interest in research and other demands
		Demands	conflicts between professional demands on time and resources
		Institution (-ve)	lack of infrastructure to support research at the institutional level
		Logistics (-ve)	factors that negatively impact the ability to conduct research as desired
		Research network (-ve)	negative aspects of belonging to a research network

	Research	**Culture:** *the behaviours and beliefs held in clinical settings regarding research*	Culture	the behaviours and beliefs held in clinical settings regarding research
			Priorities	differing stakeholder priorities: impact of research on workplace demands
			Colleagues (-ve)	negative influence of colleagues on the research process
			Independence	lack of cohesiveness in the relationships between different stakeholders as a results of groups functioning independently of one another
			Research exposure	how exposure to research shapes future perceptions
			Use of research	putting research findings into practice
		Pediatric-specific challenges: *challenges specific to the context of conducting pediatric trials (1. direct age-related issues; 2. paternalism; 3. lack of interest; 4. rarity of disease)*	Pediatric-specific challenges	challenges specific to the context of conducting pediatric trials
			Recruitment	factors that impact the recruitment of study participants
	Policy	**Administration:** *bureaucratic processes that are viewed as obstructionistic to research*	Ethics (-ve)	barriers imposed by the ethics review process
			Financial incentive	lack of economic incentives to conduct pediatric trials
			Priorities	differing stakeholder priorities: budgetary considerations

FACILITATORS	Personal	**Acceptance:** *integration of the researcher into the clinical setting*	Perception of research team	how researchers are viewed by the clinicians participating in their trials
		Emotional investment: *personal dedication to research to improve care for children*	Personal stake	personal interest or involvement of the investigators in conducting research
			Priorities	differing stakeholder priorities: to improve care of children
	Environmental	**Infrastructure:** *the underlying framework or features of an organization that are conducive to the conduct of research*	Institution (+ve)	factors put in place at the institutional level to support research
	Research	**Cohesive Study Team:** *a study team that has the appropriate expertise and the available staff to successfully complete a trial*	Delegating (+ve)	the ability to assign research tasks to qualified individuals to take them out of the hands of the clinicians
			Balance	balance between clinical reality and scientific rigor
			Adoption	ongoing use of methods to minimize risk of bias
			Colleagues (+ve)	positive influence of colleagues on the research process
			Study conduct - personnel	people involved in the conduct of the trial

		Study design - personnel	people involved in protocol development
	Verification: *resources to help improve the scientific quality of a study*	Checks and balances	checks that exist to monitor scientific quality
	Ownership: *the commitment of the investigator to engage team members, generate enthusiasm, and explain the rationale for the methodology*	Education about bias	opportunity to explain rationale for trial design and conduct
		Generating support	methods to encourage buy-in from stakeholders in the clinical research process
OTHER		Consequences	consequences of not conducting high quality trials
		Deviations from protocol	explanations for changes to the study protocol when put into practice
		Future intervention	relevant to the development of a KT intervention
		Mentorship	guidance within the research team on the design and conduct of RCTs

Appendix M. Search strategies

LITERATURE SEARCH—Social Media in Health Care

Search Summary:

Database	Date Searched	Number Retrieved	After Duplicate Removal
Medline*	13 January 2012	5,468	5,463
CENTRAL	13 January 2012	13	8
ERIC	13 January 2012	1,440	1,386
PubMed	13 January 2012	217	144
CINAHL*	13 January 2012	1,541	1,499
Academic Search Complete$	13 January 2012	1,894	1,624
Alt Health Watch$	13 January 2012	796	771
Health Source$	13 January 2012	698	673
Communication and Mass Media Complete$	17 January 2012	956	890
Web of Knowledge	13 January 2012	1,319	979
ProQuest	13 January 2012	23	22
Total		**14,365**	**13,459**

* = Databases with validated SD filters that have been applied to the results; $= limit to peer review (database function); CENTRAL contains only RCTs and does not require a filter

Database: Medline via Ovid <1946 to Present>
Search Title: Social Media Scoping Review 1.4 all SD filters | Medline – 15Dec2011 – AM
Date Searched: 13 January 2012
Limits: Year of publication ≥2000; RCT/CCT, SR, observational, qualitative study filters applied
Results: 5,468 (Ovid duplicate removal function applied)

Internet and social media related MeSH [Medical Subject Headings]
1. exp Internet/
2. Electronic Mail/
3. Mass Media/td, ut
4. Hypermedia/
5. Online Systems/td, ut
6. Medical Informatics/
7. User-Computer Interface/
8. Computer-Assisted Instruction/
9. Computers/td, ut
10. Search Engine/
11. Computer Communication Networks/
12. Information Dissemination/

13. Therapy, Computer-Assisted/ 14. "Marketing of Health Services"/ 15. Social Marketing/ 16. exp Social Environment/ 17. **Internet.mp. and (or/12-16)** [Internet combined with broader social network/computer terms]
Internet and social medial related keywords 18. (digital adj5 platform*).mp. 19. (website* or web site* or webpage* or web page*).mp. 20. Googl*.mp. 21. Facebook*.mp. 22. YouTube.mp. 23. Second Life.mp. 24. PatientsLikeMe.mp. 25. WebMD.mp. 26. elluminate.mp. 27. flickr.mp. 28. moodle.mp. 29. picsearch.mp. 30. skype.mp. 31. ustream.mp. 32. zotero.mp. 33. ((e or electronic) adj3 newsletter*).mp. 34. (viral adj5 market*).mp. 35. (banner adj5 ad*).mp. 36. ("Web 2.0" or "Web 2").mp. 37. "Health 2.0".mp. 38. "Medicine 2.0".mp. 39. (Social adj3 network*).mp. 40. linkedin.mp. 41. blog*.mp. 42. wiki*.mp. 43. podcast*.mp. 44. really simple syndicat*.mp. 45. (rss adj3 (reader* or feed*)).mp. 46. (forum* adj3 (internet or web* or chat*)).mp. 47. content communit*.mp. 48. user generated content.mp. 49. microblog*.mp. 50. (twitter or tweet*).mp. 51. (("peer to peer" adj5 network*) or P2P).mp. 52. (social adj3 media*).mp. 53. i-phone*.mp. 54. myspace.mp. 55. smartphone*.mp.
56. **or/1-11,17-55** [Internet/social media MeSH and keywords] (**92,578**)

Health care education/promotion terms 57. exp Health/ 58. "Delivery of Health Care"/ 59. health behavior/ 60. exp Health Education/ 61. exp Health Promotion/ 62. Patient Care/ 63. Patient Participation/ 64. medical education/ 65. ((patient* or physician* or nurse* or pharm* or "health care profession*") adj2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)).mp.
66. **or/57-65** [Health promotion/health outcome terms] (**624,172**)
67. **and/56,66** [social media + health promotion/outcome terms] (**15,219**)

Search filters to stream out non-research papers

RCT Filter 68. randomized controlled trial.pt. 69. controlled clinical trial.pt. 70. randomized.ab. 71. placebo.ab. 72. exp Clinical Trials as Topic/ 73. randomly.ab. 74. trial.ti. 75. or/68-74 76. exp animals/ not humans.sh. 77. **75 not 76** [Cochrane RCT filter to max sensitivity and precision] (**730,963**)
SR Filter 78. meta analysis.mp,pt. 79. review.pt. 80. search*.tw. 81. **or/78-80** [HIRU SR filter to balance sensitivity and specificity] (**1,779,109**)
Observational Study Filter 82. epidemiologic studies/ 83. exp Case-Control Studies/ 84. exp Cohort Studies/ 85. case control.tw. 86. (cohort adj (study or studies)).tw. 87. cohort analy*.tw. 88. (follow up adj (study or studies)).tw. 89. (observational adj (study or studies)).tw. 90. longitudinal.tw. 91. retrospective.tw. 92. cross sectional.tw. 93. Cross-Sectional Studies/ 94. **or/82-93** [SIGN observational study filter] (**1,508,983**)
Qualitative Research Filter

95. interview*.tw. 96. experience*.mp. 97. qualitative.tw. 98. **or/95-97** [HIRU qualitative study filter] (**756,921**)
99. or/77,81,94,98 [combination of all search filters] (**4,143,826**)
100. and/67,99 [combination of social media terms + health ed terms + SD filters] (**6,589**)
101. limit 100 to humans (**6,234**) 102. limit 101 to yr="2000 -Current" (**5,524**) 103. remove duplicates from 102 (**5,468**)

Database: CENTRAL
Search Title: Social Media Scoping Review 2.0 |CENTRAL -- 23 Dec 2011 -- AM
Date Searched: 13 January 2012
Limits: Year of publication ≥2000
Results: 13

Internet and social media related MeSH: 1. exp Computer Communication Networks/ 2. Electronic Mail/ 3. Mass Media/ 4. hypermedia/ 5. exp Online Systems/ 6. exp Medical Informatics/ 7. user-computer interface/ 8. Computer-Assisted Instruction/ 9. Computers/ 10. Search Engine/ 11. Information Dissemination/ 12. exp Therapy, Computer-Assisted/ 13. "Marketing of Health Services"/ 14. social marketing/ 15. exp social environment/ 16. **internet.mp. and (or/11-15)** [Internet combined with broader social network/computer temrs]
Internet and social medial related keywords: 17. (digital adj3 platform*).mp. 18. (website* or web site* or webpage* or web page*).mp. 19. googl*.mp. 20. YouTube.mp. 21. second life.mp. 22. (Facebook or Patientslikeme or webMD or elluminate or flickr or moodle or picsearch or ustream or zotero or linkedin or myspace).mp. 23. ((e or electronic) adj3 newsletter*).mp. 24. (viral adj5 market*).mp. 25. (banner adj5 ad*).mp.

26. ("Web 2.0" or "Web 2").mp. 27. "Health 2.0".mp. 28. "Medicine 2.0".mp. 29. (social adj5 network*).mp. 30. blog*.mp. 31. wiki*.mp. 32. podcast*.mp. 33. (really simple syndicat* or (rss adj5 (reader* or feed*))).mp. 34. (forum* adj5 (internet or web* or chat*)).mp. 35. (content adj3 communit*).mp. 36. user generated content.mp. 37. microblog*.mp. 38. (twitter or tweet*).mp. 39. (("peer to peer" adj5 network*) or P2P).mp. 40. (social adj3 media*).mp. 41. i-phone*.mp. 42. smartphone*.mp.
43. **or/1-10,16-42** [Internet/social media MeSH and keywords]
Health care education/promotion terms: 44. exp health/ 45. exp "Delivery of Health Care"/ 46. exp Health Behavior/ 47. exp Health Education/ 48. exp Health Promotion/ 49. exp Patient Care/ 50. Patient Participation/ 51. exp Education, Medical/ 52. ((patient* or physician* or doctor* or nurse* or pharm* or "health care profession*") adj2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)).mp.
53. **or/44-52** [health promotion/health education/outcome terms]
54. **and/43,53** [social media terms + health promotion/outcome terms]
55. limit 54 to medline records
56. **54 not 55** [removal of medline records]

Database: ERIC via Ovid <1965 to April 2012>
Search Title: Social Media Scoping Review 3.0 | ERIC -- 13 Jan 2012 -- AM
Date Searched: 13 January 2012
Limits: Year of publication ≥2000
Results: 1,440

Internet and social media related index terms: 1. internet/ 2. electronic mail/ 3. mass media/ 4. hypermedia/ 5. exp online systems/

6. computer assisted instruction/
7. computers/
8. search engines/
9. online searching/
10. gateway systems/
11. information technology/
12. information dissemination/
13. marketing/
14. **internet.mp. and (or/11-13)** [Internet combined with broader information/marketing terms]

Internet and social medial related keywords:
15. (digital adj5 platform*).mp.
16. ("website*" or "web site*" or "webpage*" or "web page*").mp.
17. Googl*.mp.
18. Facebook*.mp.
19. youtube.mp.
20. Second Life.mp.
21. patientslikeme.mp.
22. webMD.mp.
23. elluminate.mp.
24. flickr.mp.
25. moodle.mp.
26. picsearch.mp.
27. skype.mp.
28. ustream.mp.
29. zotero.mp.
30. ((e or electronic) adj3 newsletter*).mp.
31. (viral adj5 market*).mp.
32. (banner adj5 ad*).mp.
33. ("Web 2.0" or "Web 2").mp.
34. "Health 2.0".mp.
35. "Medicine 2.0".mp.
36. (social adj3 network*).mp.
37. linkedin.mp.
38. blog*.mp.
39. wiki*.mp.
40. podcast*.mp.
41. really simple syndicat*.mp.
42. (rss adj3 (reader* or feed*)).mp.
43. (forum* adj3 (internet or web* or chat*)).mp.
44. content communit*.mp.
45. user generated content.mp.
46. microblog*.mp.
47. (twitter or tweet*).mp.
48. (("peer to peer" adj5 network*) or P2P).mp.
49. (social adj3 media).mp.

50. i-phone*.mp. 51. smartphone*.mp. 52. myspace.mp.
53. **or/1-10,14-52** [Internet/social media indexed terms + keywords]
Health care education/promotion terms: 54. exp health/ 55. health behavior/ 56. health education/ 57. exp Medical Education/ 58. health promotion/ 59. allied health occupations education/ 60. ((patient* or physician* or doctor* or nurse* or pharm* or "health care profession*") adj2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)).mp.
61. **or/54-60** [health promotion/education outcome terms]
62. **and/53,61** [social media + health promotion/education outcomes]
63. limit 62 to yr="2000 -Current"
64. remove duplicates from 63

Database: CINAHL Plus with Full Text
Search Title: Social Media -- Cinahl 13 Jan 2012 -- Complete w/ SD and yr filters
Date Searched: 13 January 2012
Limits: Year of publication ≥2000
Results: 1,541

S110=S109 Limiters - Published Date from: 20000101-20120131 S109=S108 Limiters - Exclude MEDLINE records
S108=**S71 and S107**
S107=**S82 or S94 or S102 or S106**
Qualitative Studies Filter for CINAHL [Qual Health Res 2007 17: 705]: S106=S103 or S104 or S105 S105=TX qualitative stud* S104=(MH "Audiorecording") S103=TX interview
Observational Studies Filter [SIGN filter]: S102=S95 or S96 or S97 or S98 or S99 or S100 or S101 S101=TX (observational N1 (study or studies)) S100=TX (cohort N1 (study or studies)) S99=(MH "Cross Sectional Studies") S98=(MH "Nonconcurrent Prospective Studies") S97=(MH "Correlational Studies") S96=(MH "Case Control Studies+") S95=(MH "Prospective Studies+")
Systematic Reviews Filter [SIGN filter]: S94=S88 NOT S93 S93=S89 or S90 or S91 or S92 S92=(MH "Animals") S91=PT editorial

S90=PT letter
S89=PT commentary
S88=S83 or S84 or S85 or S86 or S87
S87=TX (systematic N1 (review OR overview))
S86=(MH "Literature Review+")
S85=TX Metaanalys*
S84=TX Meta analys*
S83=(MH "Meta Analysis")

Randomized Controlled Trials Filter [SIGN filter]:
S82=(S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80 or S81)
S81=TX allocat* random*
S80=MH "Quantitative Studies"
S79=MH "Placebos"
S78=TX placebo*
S77=TX random* allocat*
S76=MH "Random Assignment"
S75=(TX ((singl* N1 blind*) OR (singl* N1 mask*))) OR (TX ((doubl* N1 blind*) OR (doubl* N1 mask*))) OR (TX ((tripl* N1 blind*) OR (tripl* N1 mask*))) OR (TX ((trebl* N1 blind*) OR (trebl* N1 mask*)))
S74=TX clinic* N1 trial*
S73=PT clinical trial
S72=(MH "Clinical Trials+")

S71=**S56 and S70**

S70=**S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69**

Health care education/promotion terms:
S69=TI "health care profession*" N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S68=TI pharm* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S67=TI nurse* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S66=TI physician* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S65=TI patient* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S64=(MH "Consumer Participation")
S63=(MH "Patient Care")
S62=(MH "Education, Health Sciences+")
S61=(MH "Health Promotion+")
S60=(MH "Health Education")
S59=(MH "Health Behavior")
S58=(MH "Health Care Delivery")
S57=(MH "Health")

S56=**S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38**

or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55
Internet and social medial related keywords: S55=TI smartphone* S54=TI myspace S53=TX i-phone* S52=TI social N3 media* S51=TI "peer to peer" N5 network* OR TI P2P S50=TI twitter OR TI tweet* S49=TX microblog* S48=TI user generated content S47=TI content communit* S46=TI forum* N3 internet OR TI forum* N3 web* OR TI forum* N3 chat* S45=TI rss N3 reader* OR TI rss N3 feed* S44=TX really simple syndicat* S43=TI podcast* S42=TI wiki* S41=TI blog* S40=TI social N3 network* S39=TX "Medicine 2.0" S38=TX "Health 2.0" S37=TI "Web 2.0" OR "Web 2" S36=TX zotero S35=TX ustream S34=TX skype S33=TX picsearch S32=TX moodle S31=TX flickr S30=TX elluminate S29=TX banner N5 ad* S28=TX viral N5 market* S27=TI e N3 newsletter* OR TI electronic N3 newsletter* S26=TI WebMD S25=TI Patients Like Me OR TI PatientsLikeMe S24=TI Second Life S23=TI youtube S22=TI facebook* S21=TI googl* S20=TI website* OR TI web site* OR TI webpage* OR TI web page* S19=TX digital N3 platform*
Internet and social media related index terms: S18=S1 AND (S17 OR S16 OR S15 OR S14) S17=(MH "Social Environment") S16=(MH "Social Marketing") S15=(MH "Health Information Management Service") S14=(MH "Therapy, Computer Assisted+")

S13=(MH "Computer Communication Networks")
S12=(MH "Computers and Computerization/TD/UT")
S11=(MH "Computer Assisted Instruction/TD/UT")
S10=(MH "User-Computer Interface")
S9=(MH "Health Informatics+")
S8=(MH "Online Services/TD/UT")
S7=(MH "Online Systems+/TD/UT")
S6=(MH "Multimedia/TD/UT")
S5=(MH "Hypertext")
S4=(MH "Hypermedia")
S3=(MH "Communications Media/TD/UT")
S2=(MH "Electronic Mail")
S1=(MH "Internet+")

Database: Academic Search Complete
Search Title: Social Media -- Acad Search Compl 13 Jan -- Complete Search + limits
Date Searched: 13 January 2012
Limits: Year of publication ≥2000
Results: 1,894

S65=S64 Limiters - Published Date from: 20000101-20120131S
S64=S63=Limiters - Scholarly (Peer Reviewed) Journals

S63=**S52 and S62**

S62=**S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61**

Health care education/promotion terms:
S61=TI "health care profession*" N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S60=TI pharm* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S59=TI nurse* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S58=TI physician* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S57=TI patient* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*)
S56=TI patient* N5 participation
S55=TI patient* N5 care
S54=TI patient* N5 satisfact*
S53=TI health

S52=**S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51**

Internet and social medial related keywords:
S51=TI Smartphone*
S50=TI myspace

S49=TI i-phone*
S48=TI social N3 media
S47=TI peer N1 network*
S46=TI twitter OR tweet*
S45=TI microblog*
S44=TI user generated content
S43=TI content communit*
S42=TI forum* N3 internet OR TI forum* N3 web* OR TI forum* N3 chat*
S41=TI rss N3 reader* OR TI rss N3 feed*
S40=TI really simple syndicat*
S39=TI podcast*
S38=TI wiki*
S37=TI blog*
S36=TI linkedin
S35=TI social N3 network*
S34=TX "Medicine 2.0"
S33=TX "Health 2.0"
S32=TI "Web 2.0" OR "web 2"
S31=TI banner N5 ad*
S30=TI viral N5 market*
S29=TI e N3 newsletter* OR TI electronic N3 newsletter*
S28=TI zotero
S27=TX ustream
S26=TI skype
S25=TX picsearch
S24=TI moodle
S23=TI flickr
S22=TI elluminate
S21=TI WebMD
S20=TI patientslikeme OR TI patients like me
S19=TI second life
S18=TI youtube*
S17=TI facebook*
S16=TI googl*
S15=TI website* OR TI "web site*" OR TI webpage* OR TI "web page*"
S14=TI digital N5 platform*
S13=TI social environment
S12=TI market* N3 social
S11=TI market* N3 health
S10=TI market* N3 "health service*"
S9=TI information dissemination
S8=TI search engine*
S7=TI computer*
S6=TI informatic*
S5=TI online N1 system* OR TI online N1 service*
S4=TI hypermedia OR TI hypertext OR TI multimedia

S3=TI mass media S2=TI electronic mail* OR TI e mail* OR TI email* S1=TI internet

Database: Alt Health Watch; Health Source
Search Title: Social Media -- Alt Health/Source 13 Jan 2012 -- Complete + limits
Date Searched: 13 January 2012
Limits: Year of publication ≥2000
Results: Alt Health Watch: 796; Health Source: 698

S61=S60 Limiters - Published Date from: 20000101-20120131 S60=S59 Limiters - Scholarly (Peer Reviewed) Journals
S59=**S48 and S58**
S58=**S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57**
Health care education/promotion terms: S57=TX pharm* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S56=TX "health care profession*" N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S55=TX nurse* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S54=TX physician* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S53=TX patient* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S52=TX patient* N1 participation S51=TX patient* N1 satisfact* S50=TX patient* N1 care S49=TX "health delivery" OR "health behaviour*" OR "health behavior*" OR "health educat*" OR "health promot*"
S48=**S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47**
Internet and social medial related keywords: S47=TX myspace S46=TX smartphone* S45=TX i-phone* S44=TX social N3 media S43=TX peer N1 network* S42=TX twitter OR tweet* S41=TX microblog* S40=TX user generated content S39=TX "content communit*" S38=TX forum* N3 internet OR TX forum* N3 web* OR TX forum* N3 chat*

S37=TX rss N3 reader* OR TX rss N3 feed*
S36=TX really simple syndicat*
S35=TX podcast*
S34=TX wiki*
S33=TX blog*
S32=TX linkedin
S31=TX social N3 network*
S30=TX "Medicine 2.0"
S29=TX "Health 2.0"
S28=TX "Web 2.0" OR "web 2"
S27=TX viral N5 market*
S26=TX e N3 newsletter* OR TX electronic N3 newsletter*
S25=TX zotero
S24=TX ustream
S23=TX skype
S22=TX picsearch
S21=TX moodle
S20=TX flickr
S19=TX WebMD
S18=TX patientslikeme OR TX "patients like me"
S17=TX "second life"
S16=TX youtube*
S15=TX facebook*
S14=TX googl*
S13=TI website* OR TI "web site*" OR TI webpage* OR TI "web page*"
S12=TX digital N5 platform*
S11=TX "social environment"
S10=TX market* N3 social
S9=TX "health market*"
S8=TX information dissemination
S7=TX search engine*
S6=TI computer*
S5=TX informatic*
S4=TX online N1 system* OR TX online N1 service*
S3=TX mass media
S2=TI "electronic mail*" OR TI "e mail*" OR TI email*
S1=TX Internet

Database: Communication and Mass Media complete
Search Title: Social Media – Communication & Mass Media 17 Jan 2012 -- Complete
Date Searched: 17 January 2012
Limits: Year of publication ≥2000
Results: 956

S61=S60 Limiters - Published Date from: 20000101-20120131

S60=S59 Limiters - Scholarly (Peer Reviewed) Journals
S59=**S48 and S58**
S58=**S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57**
Health care education/promotion terms: S57=TX pharm* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S56=TX "health care profession*" N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S55=TX nurse* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S54=TX physician* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S53=TX patient* N2 (teach* or train* or instruction* or intervention* or program* or inform* or educat* or outcome*) S52=TX patient* N1 participation S51=TX patient* N1 satisfact* S50=TX patient* N1 care S49=TX "health delivery" OR "health behaviour*" OR "health behavior*" OR "health educat*" OR "health promot*
S48=**S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47**
Internet and social medial related keywords: S47=TX myspace S46=TX smartphone* S45=TX i-phone* S44=TI social N3 media S43=TX peer N1 network* S42=TX twitter OR tweet* S41=TX microblog* S40=TX user generated content S39=TX "content communit*" S38=TX forum* N3 internet OR TX forum* N3 web* OR TX forum* N3 chat* S37=TX rss N3 reader* OR TX rss N3 feed* S36=TX really simple syndicat* S35=TX podcast* S34=TX wiki* S33=TI blog* S32=TX linkedin S31=TI social N3 network* S30=TX "Medicine 2.0" S29=TX "Health 2.0" S28=TX "Web 2.0" OR "web 2" S27=TX viral N5 market*

S26=TX e N3 newsletter* OR TX electronic N3 newsletter*
S25=TX zotero
S24=TX ustream
S23=TX skype
S22=TX picsearch
S21=TX moodle
S20=TX flickr
S19=TX WebMD
S18=TX patientslikeme OR TX "patients like me"
S17=TX "second life"
S16=TX youtube*
S15=TX facebook*
S14=TX googl*
S13=TI website* OR TI "web site*" OR TI webpage* OR TI "web page*"
S12=TX digital N5 platform*
S11=TX "social environment"
S10=TX market* N3 social
S9=TX "health market*"
S8=TX information dissemination
S7=TI search engine*
S6=TI computer*
S5=TX informatic*
S4=TX online N1 system* OR TX online N1 service*
S3=TI mass media
S2=TI "electronic mail*" OR TI "e mail*" OR TI email*
S1=TX Internet

Database: PubMed via NLM
Search Title:
Date Searched: 13 January 2012
Limits: Last 180 days; humans
Results: 217

(("Education, Medical"[Mesh]) OR ("Patient Participation"[Mesh]) OR ("Patient Care"[Mesh:noexp]) OR ("Health Promotion"[Mesh]) OR ("Health Education"[Mesh]) OR ("Health Behavior"[Mesh:noexp]) OR ("Delivery of Health Care"[Mesh:noexp]) OR ("Health"[Mesh])) AND (("Internet"[Mesh]) OR ("Electronic Mail"[Mesh]) OR ("Mass Media/trends"[Mesh:noexp] OR "Mass Media/utilization"[Mesh:noexp]) OR ("Hypermedia"[Mesh]) OR ("Online Systems/trends"[Mesh] OR "Online Systems/utilization"[Mesh]) OR ("Medical Informatics"[Mesh:noexp]) OR ("User-Computer Interface"[Mesh]) OR ("Computer-Assisted Instruction"[Mesh]) OR ("Computers/trends"[Mesh:noexp] OR "Computers/utilization"[Mesh:noexp]) OR ("Search Engine"[Mesh]) OR ("Computer Communication Networks"[Mesh:noexp]) OR ((internet) AND (((((("Information Dissemination"[Mesh]) OR "Therapy, Computer-Assisted"[Mesh:noexp]) OR "Marketing of Health Services"[Mesh]) OR "Social

Marketing"[Mesh]) OR "Social Environment"[Mesh])) OR (website* OR "web site*" OR webpage* OR "web page*") OR (googl*) OR (youtube) OR (facebook*) OR ("second life") OR ("Web 2.0" OR "Web 2") OR (social media OR social network*) OR (blog*) OR (wiki*) OR (podcast*) OR (internet forum OR chat forum OR web forum) OR (twitter OR tweet*) OR ("peer to peer network*" OR "P2P"))

Database: Web of Knowledge (1898-present)
Search Title: Social Media 13 Jan
Date Searched: 13 January 2012
Limits: Year of publication ≥2000
Results: 1,319

19=#17 AND #13
Refined by: Publication Years=(2010 OR 2002 OR 2011 OR 2001 OR 2009 OR 2008 OR 2007 OR 2006 OR 2004 OR 2005 OR 2000 OR 2012 OR 2003)
18=#17 AND #13
17=#16 OR #15 OR #14
16=Title=(education)
15=Title=(patient)
14=Title=(health)
13=#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
12=Title=(Twitter OR tweet*)
11=Title=(podcast*)
10=Title=(wiki*)
9=Title=(blog*)
8=Title=("Web 2.0" OR "Web 2")
7=Title=(YouTube)
6=Title=(Facebook*)
5=Title=(Googl*)
4=Title=(webpage* OR "web page*" OR website* OR "web site*")
3=Title=("Search Engine*")
2=Title=("e mail" OR "e-mail" OR "electronic mail")
1=Title=(Social Media)

Database: Proquest
Title of Search: None
Date Searched: 13 Jan 2012
Limits: None
Results: 23

Citation and Abstract = Social Media AND Citation and Abstract = health OR patient

Appendix N. Screening criteria

Screening Criteria (Level I)

Reviewer:			**Ref ID:**
CRITERIA	**Yes**	**No**	**Unclear**
1. PUBLICATION TYPE			

Report of primary research:
• Quantitative
  o RCT
  o NRCT
  o Cohort
  o Cross-sectional
• Qualitative
• Mixed methods
*EXCLUDE editorials, letters, opinion pieces, reviews. Please flag systematic reviews in the screening form.
	☐	☐	☐

2. POPULATION/SETTING			
Use of social media tool in a health care setting: • Health care providers • Health care trainees	☐	☐	☐
3. INTERVENTION			
SOCIAL MEDIA is a group of online applications that allow for the creation and exchange of content generated by users. Social media tool belonging to one of the following categories*: • Collaborative project (e.g., Wikipedia) • Blog or microblog (e.g., Twitter) • Content community (e.g., YouTube) • Social networking site (e.g., Facebook) • Virtual world (e.g., Second Life) *EXCLUDE mobile health when it concerns the use of apps or use for information seeking.	☐	☐	☐
REVIEWER'S DECISION:	**Include** ☐	**Exclude** ☐	**Unsure** ☐

Inclusion Criteria (Level II Screening)

Reviewer:	**Ref ID:**		
	Yes	**No**	**Unclear**
1. PUBLICATION TYPE			
Report of primary research	☐	☐	☐
2. POPULATION/SETTING			
Use of social media tool by any population in a health care setting, e.g.: • Patient population with any condition or disease diagnosed by a health care provider • Caregivers (e.g., parents, families, other non-professional caregivers) • Health care providers or trainees	☐	☐	☐
3. INTERVENTION			
Social media tool; both: i. Administered online ii. Content generated by users (i.e., "allows for continuous modification by all users in a participatory and collaborative fashion")[7]	☐	☐	☐

Notes:
Eligible social media formats:
*"Enables and facilitates social networking, participation, apomediation, collaboration, and openness within and between user groups." (Eysenbach JMIR 2008)
*Online discussions are eligible if there is a searchable record of the conversation (i.e., chat rooms could be eligible, instant messaging would not).
*Formats enable one-to-many (e.g., blogs, Twitter) or many-to-many (e.g., Facebook) postings between users, NOT one-to-one (e.g., email).

Ineligible formats:
*electronic medical records
*tailored feedback that only includes an automated/computer-generated report based on certain parameters

Comments:

REVIEWER'S DECISION: **Include** ☐ **Exclude** ☐ **Unsure** ☐

If included:

Population:
Patient ☐
Caregiver ☐
Health care provider ☐

Study design:
Quantitative ☐
Qualitative ☐
Both ☐

Disease/condition(s) studied: _____

Appendix O. Data extraction form

Variable	Response	Comments
RefID		-highlighted in red: likely exclude, but double-check (chat rooms, podcasts) -highlighted in orange: check comments at end of form
Author, Year		
Reviewer 1 (DE)	(reviewer's initials)	DE: data extraction
Reviewer 2 (DV)	(reviewer's initials)	DV: data verification
Study Characteristics		
Country (publication)		List country of corresponding author Use USA and UK as abbreviations
Country (involved)		List country or countries involved in study Use USA and UK as abbreviations
Study dates		Month Year – Month Year (e.g., November 2006 – October 2007)
Publication type	-Journal article -Abstract -Dissertation	-if the study is a non-English article with an English abstract, classify as an abstract and extract any relevant information from there
Language	-English -Non-English	-refers to the full text (relevant for included studies with an English abstract)
Study design	-Quantitative -Qualitative -Mixed methods (specify)	
	-RCT -NRCT -Prospective cohort -Retrospective cohort -Cross-sectional	-for quantitative studies, refer to algorithm for study designs (*Hartling et al. J Clin Epi 2011*) -for qualitative studies, refer to overview of qualitative designs (http://www.southalabama.edu/coe/bset/johnson/lectures/lec12.htm)

	-Phenomenology -Ethnography -Case study -Grounded theory -Other (specify)	
Method of data collection		Specify how data was collected, e.g., survey, interviews, etc.
Sample size		Report actual sample size
Population Characteristics		
Discipline or specialty studied		
Target population		Describe who they intended to study, e.g., middle-aged women, children, etc.
Intervention Characteristics		
Intervention (select all that apply)		-for intervention classifications, refer to section 3 of *Kaplan and Haenlein Bus Horiz 2010*
	-Collaborative project	Enables the joint and simultaneous creation of content by many end-users. Includes things like wikis (Wikipedia) and social bookmarking applications (Mendeley).
	-Blog or microblog	Websites that display date-stamped entries. They are usually managed by one person but provide the opportunity to interact with others through the addition of comments. Includes things like Blogger (blog) and Twitter (microblog).
	-Content community	Allows for the sharing of media content between users, including text, photos, videos, and PowerPoint presentations. Examples include BookCrossing, Flickr, YouTube, and SlideShare.
	-Social networking site	Enables users to connect by creating personal information profiles that can be accessed by friends and colleagues, and by sending emails and instant messages between each other. Includes Facebook, MySpace, and LinkedIn.
	-Virtual world	Platforms that replicate a 3D environment in which users can

		appear in the form of personalized avatars and interact with each other as they would in real life. -Game worlds require users to behave according to rules in the context of a massively multiplayer online role-playing game. (World of Warcraft) -Social worlds allow inhabitants to essentially live a virtual life similar to their real life through the actions and interactions of their avatars. (Second Life)
	-Other (specify)	-put discussion boards, etc. in the "other" category
	-Check if part of a complex intervention	-complex interventions are those that include several components (*Campbell et al. BMJ 2000*)
Describe intervention		*[type of tool, e.g., blog]:* Provide specific details about the social media tool and how it is being used.
Objective of the intervention (select all that apply)		-Use for the **intended purpose(s)** of the social media tool -for more details, refer to *Coulter and Ellins BMJ 2007*
	-To improve knowledge	
	-To improve clinical skills	
	-To improve communication	
	-Other (specify)	
Outcomes Reported (select all that apply)		

****ONLY EXTRACT REPORTED, NOT INTENDED, OUTCOMES****

Tips: For qualitative studies, look for things like the questions they use to guide their interviews and the themes that they report in the Results section.

Clinicians' knowledge	-Knowledge of condition and complications	Formally assessed in some way, e.g., measurement of performance.
	-Knowledge of treatment options and likely outcomes	Formal assessment.

	-Comprehension of information	Formal evaluation of comprehension, e.g., quiz.
	-Recall of information	Formal evaluation of recall, e.g, quiz.
Clinicians' experience	-Clinicians' satisfaction	Assessment of attitudes: survey, interview question, etc.
	-Clinician-patient communication	
	-Clinician-public communication	E.g., online medical resources.
	-Instructor-student communication	
	-Peer-peer communication	Communication between clinicians.
Health behaviour and status	-Clinical skills	
	-Guideline adherence	Alignment of professional practices with appropriate care: following clinical practice guidelines, etc.
	-Clinical indicators	A measure, process, or outcome used to judge a particular clinical situation and indicate whether the care delivered was appropriate, e.g., proportion of diabetes patients receiving foot care, blood pressure results for hypertensive patients. *Mainz In J Qual Health Care 2003*
	-Professional/personal boundaries	E.g. friending patients on Facebook
Other outcomes (specify)		
Conclusions		
Classify conclusions	-Positive -Negative -Neutral -Indeterminate	Positive: authors stated that there is evidence of utility Negative: authors advised against the use of the intervention Neutral: no evidence of utility/authors reported no opinion Indeterminate: authors stated there is insufficient evidence *Tricco et al. J Clin Epi 2009*

	*Assess based on the authors' conclusions re: the entire intervention if social media is just one component.
Comments	
Double check	Flag (and specify) any items where you'd like a second opinion

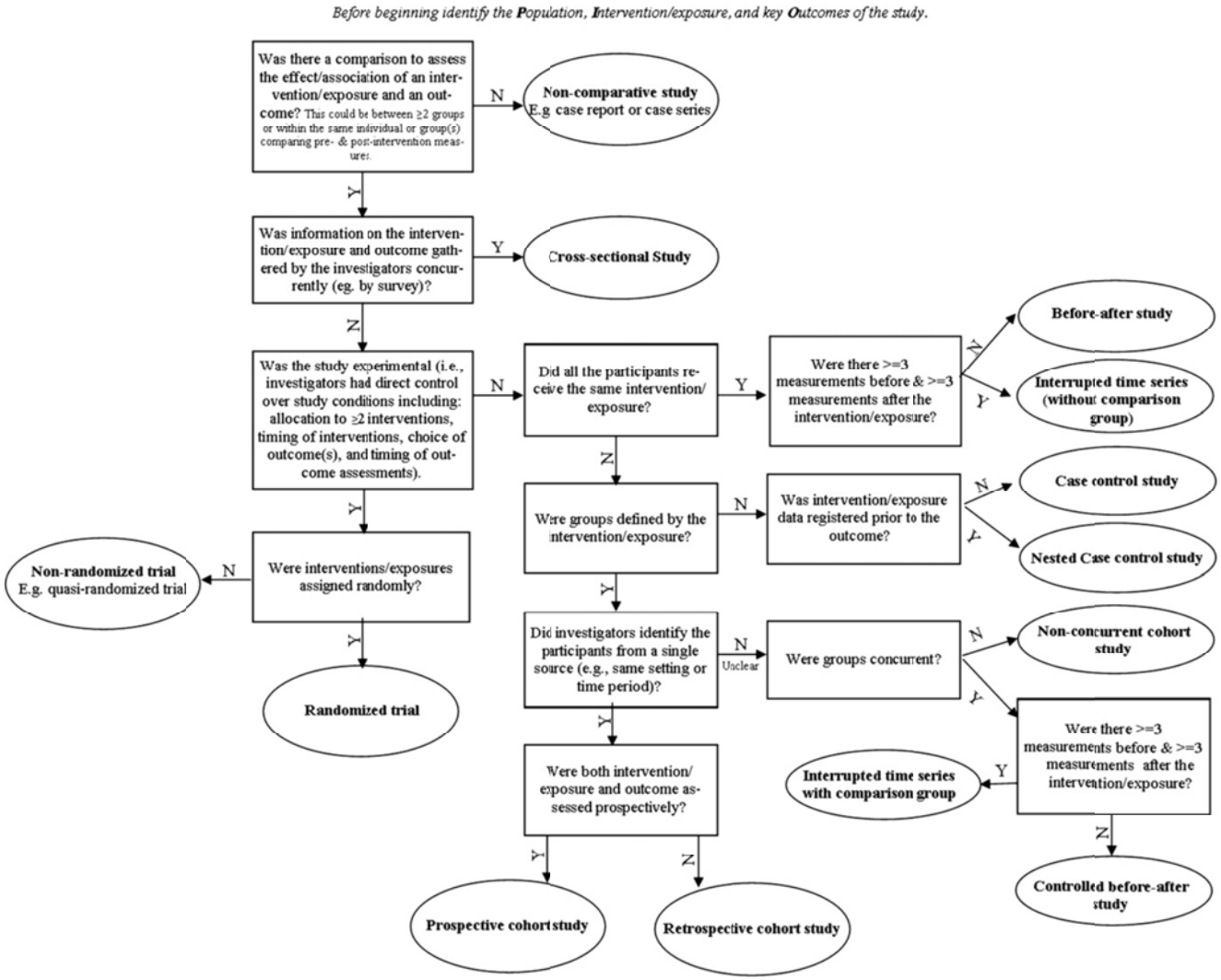

Before beginning identify the Population, Intervention/exposure, and key Outcomes of the study.
Was there a comparison to assess the effect/association of an intervention/exposure and an outcome? This could be between ≥2 groups or within the same individual or group(s) comparing pre- & post-intervention measures.
N
Non-comparative study
E.g case report or case series
Y
Was information on the intervention/exposure and outcome gathered by the investigators concurrently (eg. by survey)?
Y
Cross-sectional Study
N
Was the study experimental (i.e., investigators had direct control over study conditions including: allocation to ≥2 interventions, timing of interventions, choice of outcome(s), and timing of outcome assessments).
N
Did all the participants receive the same intervention/ exposure?
Y
Were there >=3 measurements before & >=3 measurements after the intervention/exposure?
N
Before-after study
Y
Interrupted time series (without comparison group)
N
Were groups defined by the intervention/exposure?
N
Was intervention/exposure data registered prior to the outcome?
N
Case control study
Y
Nested Case control study
Y
Were interventions/exposures assigned randomly?
N
Non-randomized trial
E.g. quasi-randomized trial
Y
Randomized trial
Y
Did investigators identify the participants from a single source (e.g., same setting or time period)?
N
Unclear
Were groups concurrent?
N
Non-concurrent cohort study
Y
Were there >=3 measurements before & >=3 measurements after the intervention/exposure?
Y
Interrupted time series with comparison group
N
Controlled before-after study
Y
Were both intervention/ exposure and outcome assessed prospectively?
Y
Prospective cohort study
N
Retrospective cohort study

TABLE 12.2 Characteristics of Four Qualitative Research Approaches

	Qualitative Research Approach			
Dimension	Phenomenology	Ethnography	Case Study	Grounded Theory
Research purpose	To describe one or more individuals' experiences of a phenomenon (e.g., the experience of the death of a loved one).	To describe the cultural characteristics of a group of people and to describe cultural scenes.	To describe one or more cases in-depth and address the research questions and issues.	To inductively generate a grounded theory describing and explaining a phenomenon.
Disciplinary origin	Philosophy.	Anthropology.	Multidisciplinary roots, including business, law, social sciences, medicine, and education.	Sociology.
Primary data-collection method	In-depth interviews with up to 10–15 people.	Participant observation over an extended period of time (e.g., one month to a year). Interviews with informants.	Multiple methods are used (e.g., interviews, observations, documents).	Interviews with 20–30 people. Observations are also frequently used.
Data analysis approach	List significant statements, determine meaning of statements, and identify the essence of the phenomenon.	Holistic description and search for cultural themes in data.	Holistic description and search for themes shedding light on the case. May also include cross-case analysis.	Begin with open coding, then axial coding, and end with selective coding.
Narrative report focus	Rich description of the essential or invariant structures (i.e., the common characteristics, or essences) of the experience.	Rich description of context and cultural themes.	Rich description of the context and operation of the case or cases. Discussion of themes, issues, and implications.	Description of topic and people being studied. End with a presentation of the grounded theory. May also list propositions.

Appendix P. Information sheet and consent form

UNIVERSITY OF ALBERTA

Department of Pediatrics/ARCHE
Faculty of Medicine & Dentistry

Edmonton Clinic Health Academy, 11405-87 Avenue
Edmonton, Alberta, Canada T6G 1C9

www.ualberta.ca
www.ualberta.ca/ARCHE

Tel: (780) 492-1078
Fax: (780) 248-5625

Study Title: A wiki-based educational resource to improve research in child health

Principal Investigator: Dr Lisa Hartling
Tel: 780.492.6124
Email: lisa.hartling@ualberta.ca

Student Investigator: Michele Hamm
Tel: 780.492.1241
Email: michele.hamm@ualberta.ca

What is the study about? The purpose of this study is to evaluate the usability of a wiki-based educational resource for researchers focusing on minimizing bias in the design and conduct of randomized controlled trials, specifically emphasizing research in pediatrics. We are interested in feedback from trialists and trainees on the content, format, and overall utility of the website, and we hope to use this information to refine the tool for evaluation on a larger scale. The time necessary to review the wiki should be approximately 30 to 60 minutes. The subsequent interview will be about some or all of the following:

- Your impressions of the content of the wiki.
- Your impressions of the format of the wiki.
- Your perceptions of the overall usability of the wiki.
- Your suggestions for improvement.

The interview will be conducted in person or by telephone. It will take about 30 to 60 minutes and will occur at a convenient time. It will be taped in order to help the researchers interpret the information accurately. Participation is voluntary and you may refuse to answer any questions, stop the interview at any time, or withdraw from the study. You can decline to discuss any topic in the interview if you wish.

Possible Benefits and Harms: The possible benefits to you for participating in this study are that you would be given access to educational materials about the methodology surrounding trials in children, potentially leading to higher quality research in pediatrics. However, you may not get any benefit from being in this research study. We anticipate minimal or no risk of harm from the research study. As a token of appreciation for your time, you will receive a $15 Starbucks gift card at the beginning of your interview, and will still receive the gift card if you decide to withdraw early from the study.

Your Privacy: All information will be held confidential (or private) and will only be accessed by members of the study team. The information that you provide will be kept in a secure area (i.e., locked filing cabinet). Your name or any other information identifying you will not be attached to the information you gave. Your name will also never be used in any presentations or publications of the study results. The data gathered from this study will be aggregated so as not to identify any person. Direct quotations may be used in the publications; however the quotations will be presented in a manner that removes any identifiable information. The information gathered for this study may be looked at again in the future to help us answer other study questions. If so, the ethics review board will first review the study to ensure the information is used ethically.

Questions: If you have questions or concerns about this study at any time, you may contact Michele Hamm at 780.492.1241 or michele.hamm@ualberta.ca.

Concerns: Please contact the University of Alberta Research Ethics Office at 780.492.2615 should you have any questions regarding your rights as a participant in a research study.

Part 1 (to be completed by the Principal Investigator):

Title of Project: A wiki-based educational resource to improve research in child health

Principal Investigator(s):	Phone Number(s):
Dr. Lisa Hartling	780.492.6124
Student Investigator:	Phone Number(s):
Michele Hamm	780.492.1241

Part 2 (to be completed by the research subject):

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the study Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your responses?	☐	☐

Who explained this study to you? _____

I agree to take part in this study: YES ☐ NO ☐

Signature_____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

Appendix Q. Interview guide

Thank you for agreeing to talk with me about your experience using this wiki. Before we start, I just wanted to ask if you have any questions about this study? Are you okay with me recording this conversation?

1. Tell me generally how you found working with the wiki.
    Probe:
        - Did you like it?
        - What did you like about it?
        - What didn't you like about it?

2. Did you find that using the wiki was straightforward?

3. How easy was the wiki to use?
    Probe:
        - Did you make or try to make any changes to the site? How easy/difficult was this?

4. How satisfied were you with the content of the wiki?
    Probe:
        - Was it informative?
        - Was it interesting?
        - Was the information easy to understand?
        - Was information consistent across the site?
        - Was the amount of content appropriate?
        - Was the level of detail appropriate?
        - Was it helpful?
        - Will this information be useful in your work?
        - Did the content meet your information-seeking needs?
        - What would you like to see in the tailored content sections?

5. How satisfied were you with the format of the wiki?
    Probe:
        - Was it well organized?
        - Was the layout an effective way of presenting the information?
        - Did you like the colour scheme?
        - How did you find navigation within the site?
        - Did this format allow you to quickly locate relevant information?
        - Was the terminology presented at an appropriate level?
        - What did you think about the interactive component?

6. Is this site consistent with what you would expect from an educational resource?
    Probe:
        - If not, what would you change?

7. Did you find the site credible?

8. Did you feel that you had sufficient control over accessing the information you wanted?

9. Did you feel that you had sufficient control over the amount of time spent on the site?

10. How convenient would this tool be as a resource for you in designing/conducting/appraising future trials?

11. Would this tool be compatible with other educational resources that you have access to (within and external to your organization)?

12. Did you increase your knowledge about minimizing bias in RCTs?

13. Would you use or recommend this tool as a resource in the future?

14. What would you change about this website? (alter/update/expand)

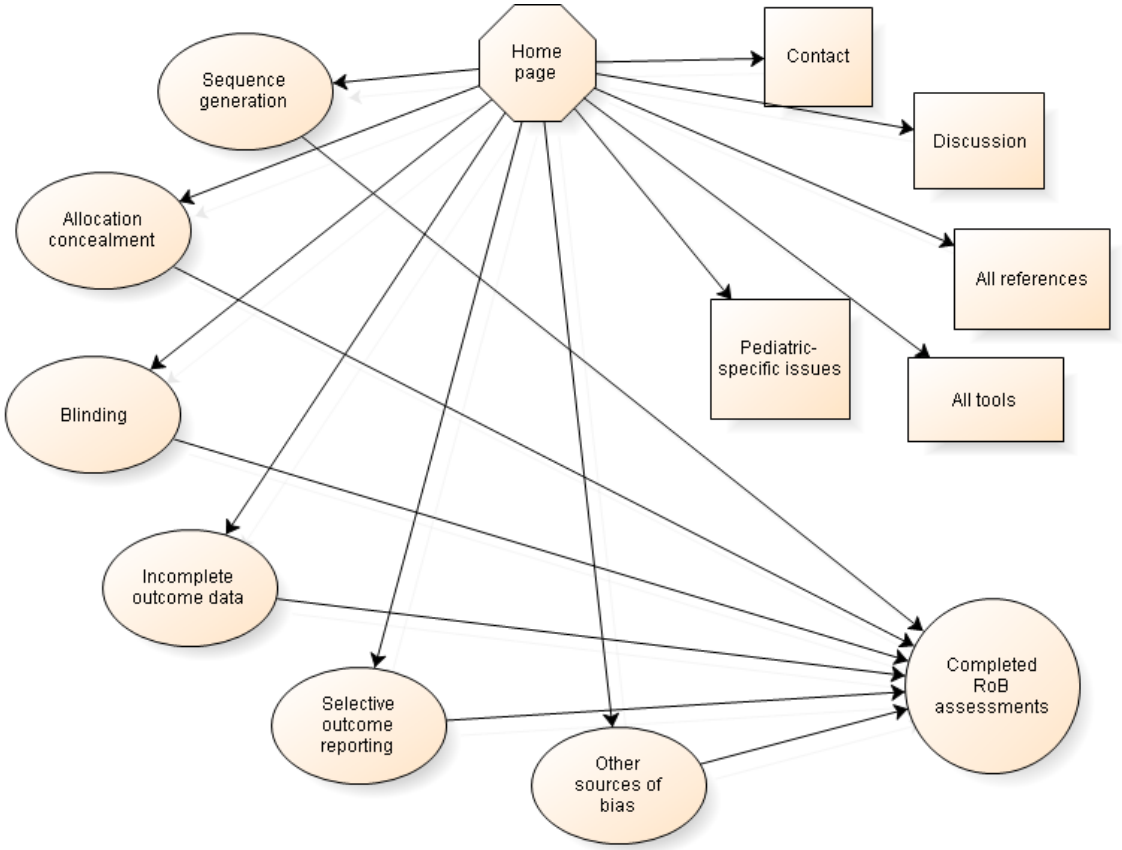
Thank you for your thoughtful answers to my questions and for taking the time to pilot test our wiki. Are there **any other comments** you would like to make that might help us to further refine our website?

May we approach you again should we have any questions about what you have told us?

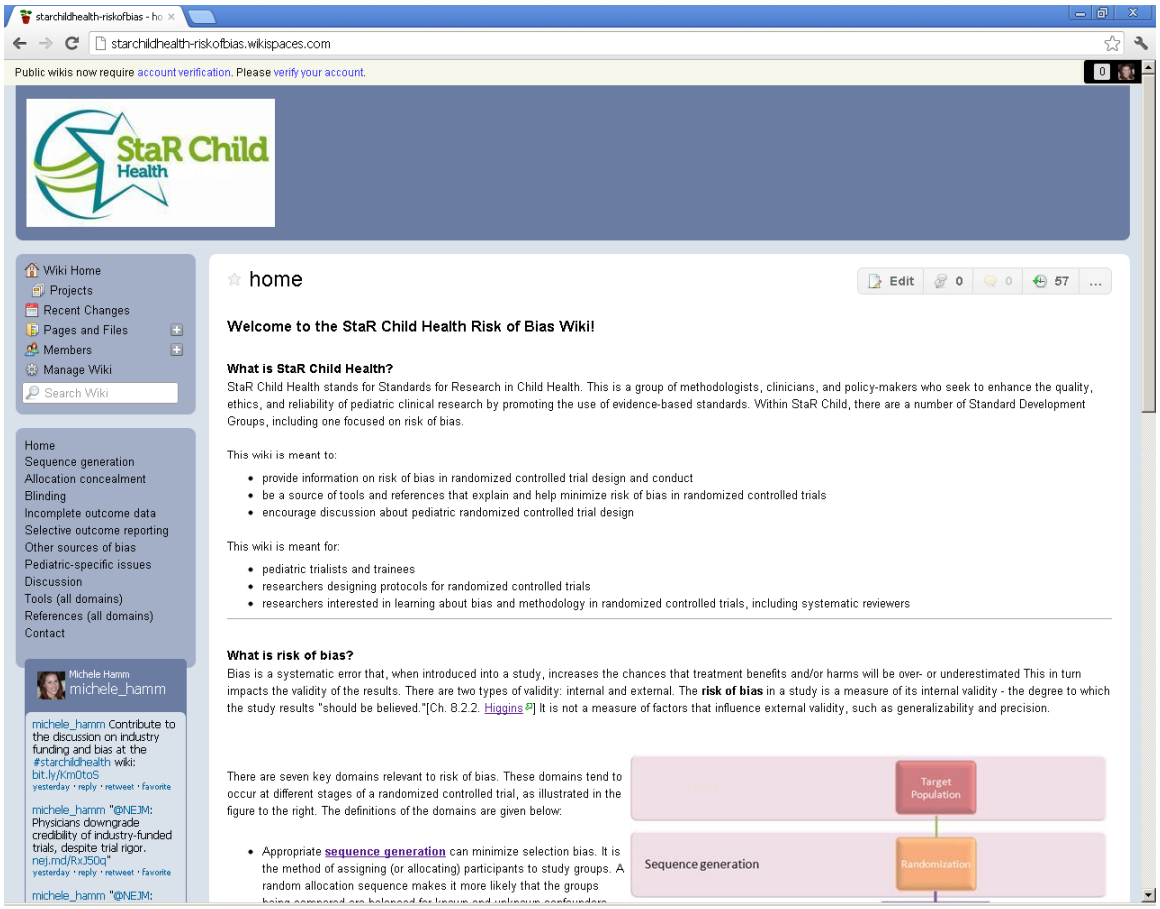
Appendix R. Interview codebook

Theme	Code	Definition
Individual pages	Home	Suggested changes for each of the individual pages
	Sequence generation	
	Allocation concealment	
	Blinding	
	Incomplete outcome data	
	Selective outcome reporting	
	Other sources of bias	
	Pediatric-specific issues	
	Discussion	
	Tools	
	References	
	Examples	
General content	General content	-Content that may go into the tailored sections for different end-users -General comments that could be incorporated into the wiki content -Ideas on examples/case studies to incorporate
	Audience	How different user groups might use the wiki (e.g., imagining the time a clinician would have to spend on it)
General formatting	General formatting	Appearance, functionality, navigation, polls/other tools that span different domain-specific pages, credibility
Preferences	Likes	Participants' comments on what they liked about the wiki
	Dislikes	Participants' comments on what they didn't like about the wiki

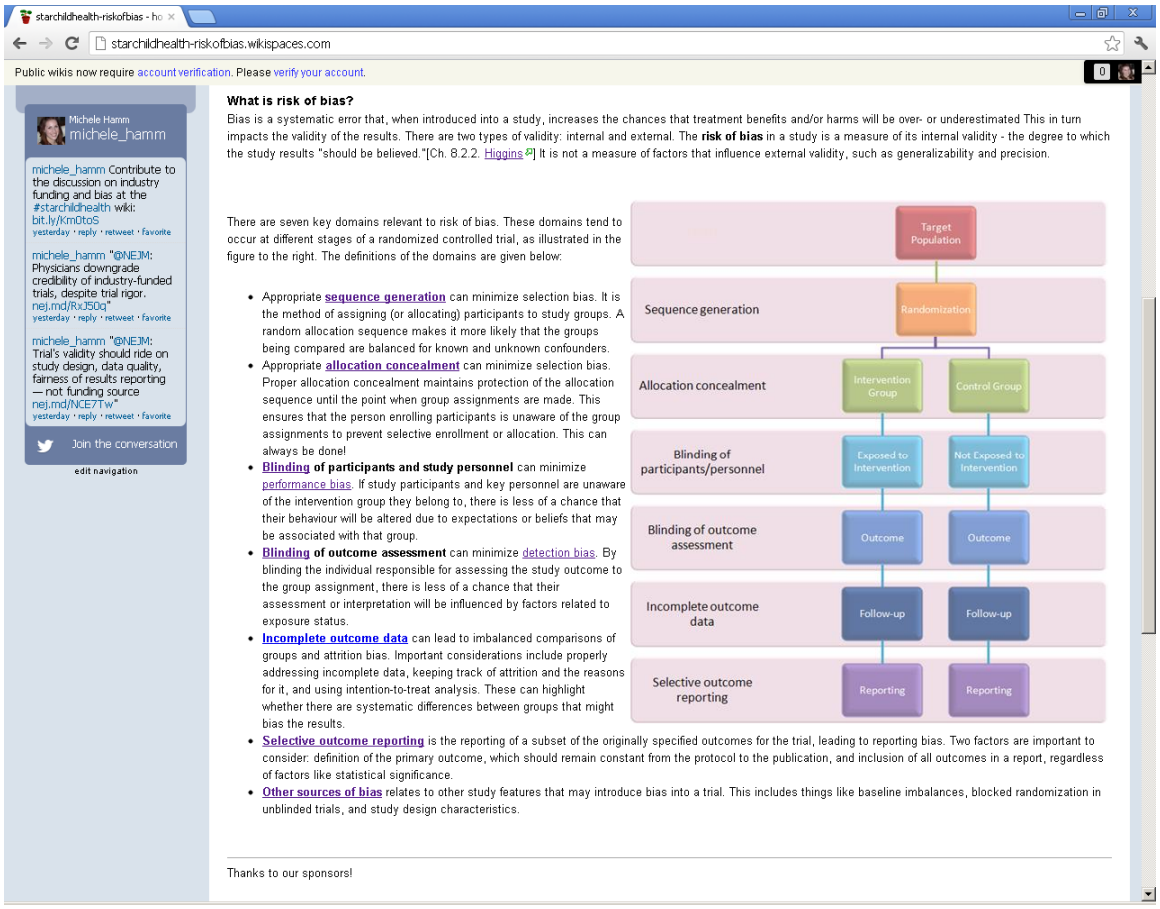
Appendix S. Wiki site map



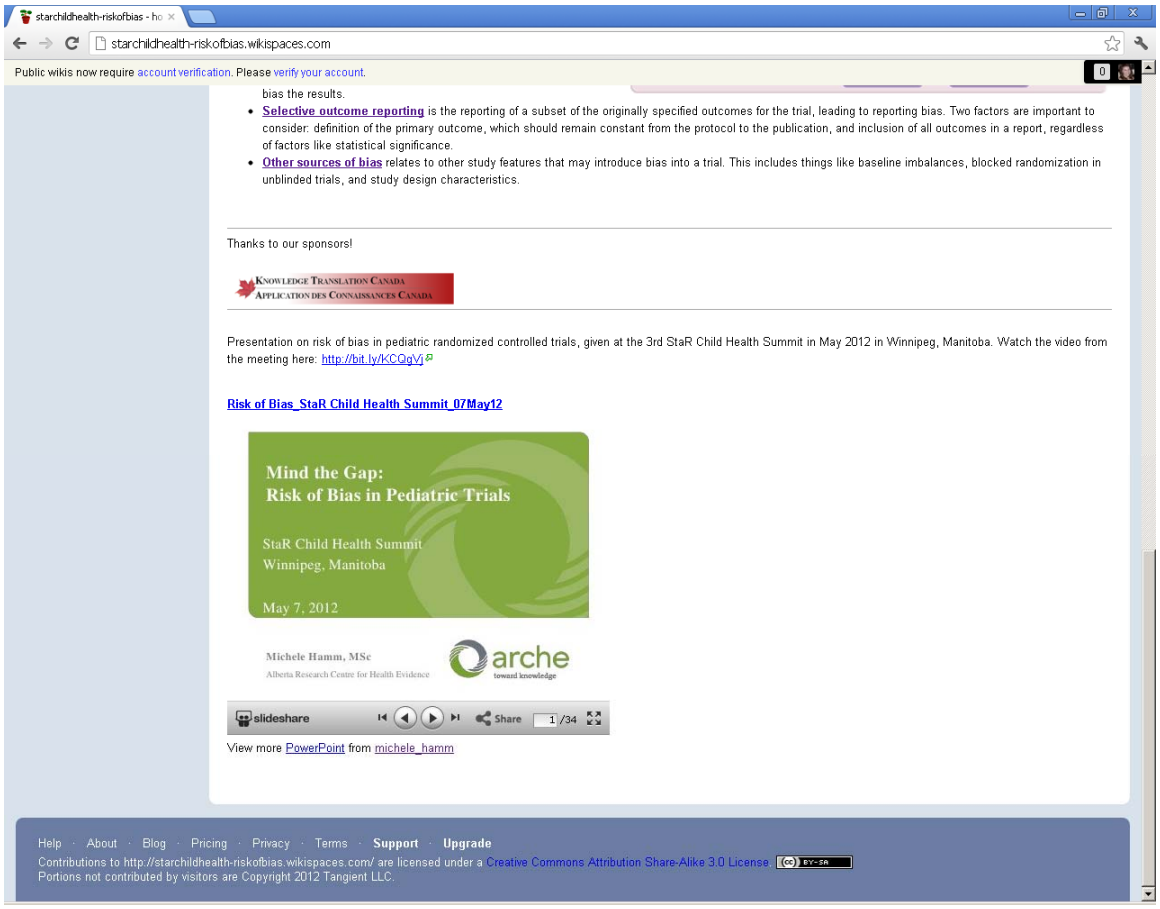
Appendix T. Wiki screen shots



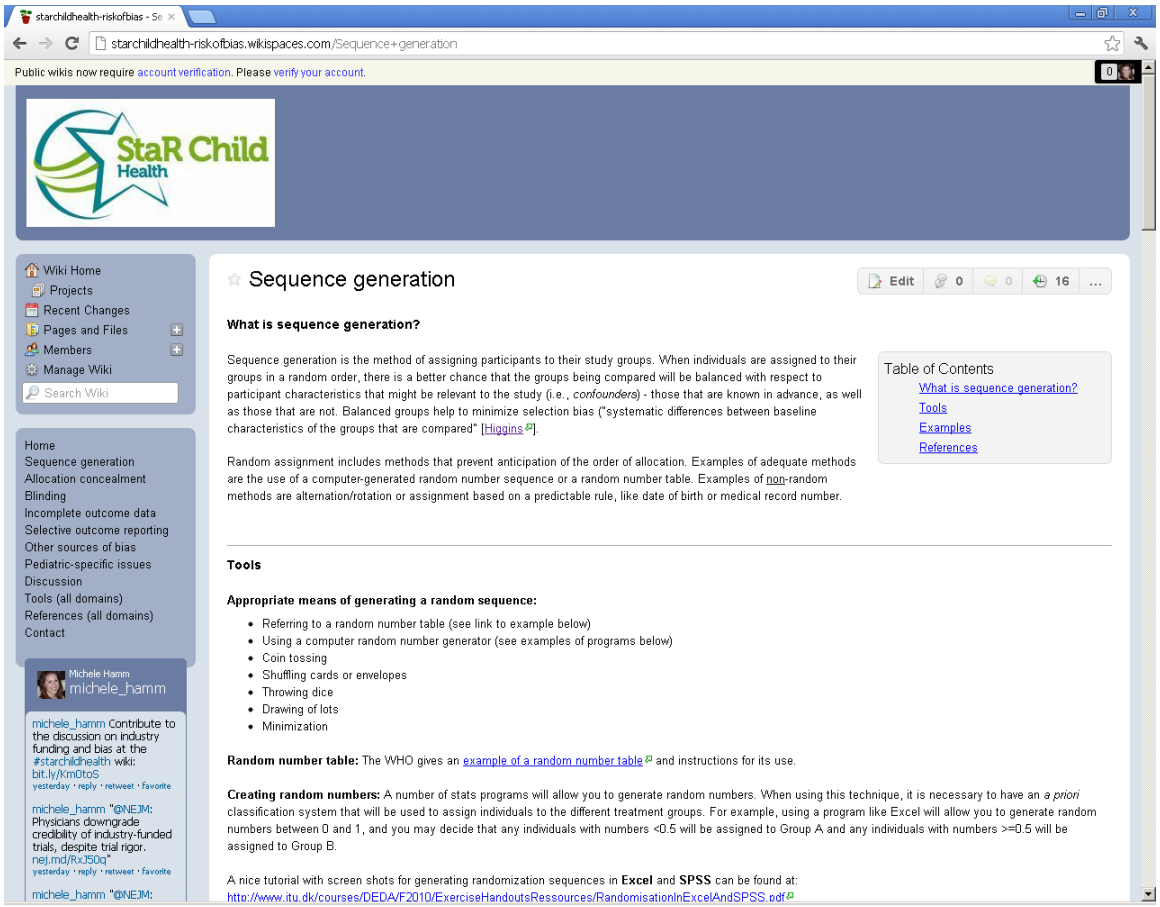
Home page


starchildhealth-riskofbias - ho
starchildhealth-riskofbias.wikispaces.com
Public wikis now require account verification. Please verify your account.
Michele Hamm
michele_hamm
michele_hamm Contribute to the discussion on industry funding and bias at the #starchildhealth wiki: bit.ly/KmOtoS
yesterday · reply · retweet · favorite
michele_hamm "@NEJM: Physicians downgrade credibility of industry-funded trials, despite trial rigor. nej.md/RxJ50q"
yesterday · reply · retweet · favorite
michele_hamm "@NEJM: Trial's validity should ride on study design, data quality, fairness of results reporting — not funding source nej.md/NCE7Tw"
yesterday · reply · retweet · favorite
Join the conversation
edit navigation
What is risk of bias?
Bias is a systematic error that, when introduced into a study, increases the chances that treatment benefits and/or harms will be over- or underestimated This in turn impacts the validity of the results. There are two types of validity: internal and external. The risk of bias in a study is a measure of its internal validity - the degree to which the study results "should be believed."[Ch. 8.2.2. Higgins] It is not a measure of factors that influence external validity, such as generalizability and precision.
There are seven key domains relevant to risk of bias. These domains tend to occur at different stages of a randomized controlled trial, as illustrated in the figure to the right. The definitions of the domains are given below:
Appropriate sequence generation can minimize selection bias. It is the method of assigning (or allocating) participants to study groups. A random allocation sequence makes it more likely that the groups being compared are balanced for known and unknown confounders.
Appropriate allocation concealment can minimize selection bias. Proper allocation concealment maintains protection of the allocation sequence until the point when group assignments are made. This ensures that the person enrolling participants is unaware of the group assignments to prevent selective enrollment or allocation. This can always be done!
Blinding of participants and study personnel can minimize performance bias. If study participants and key personnel are unaware of the intervention group they belong to, there is less of a chance that their behaviour will be altered due to expectations or beliefs that may be associated with that group.
Blinding of outcome assessment can minimize detection bias. By blinding the individual responsible for assessing the study outcome to the group assignment, there is less of a chance that their assessment or interpretation will be influenced by factors related to exposure status.
Incomplete outcome data can lead to imbalanced comparisons of groups and attrition bias. Important considerations include properly addressing incomplete data, keeping track of attrition and the reasons for it, and using intention-to-treat analysis. These can highlight whether there are systematic differences between groups that might bias the results.
Selective outcome reporting is the reporting of a subset of the originally specified outcomes for the trial, leading to reporting bias. Two factors are important to consider: definition of the primary outcome, which should remain constant from the protocol to the publication, and inclusion of all outcomes in a report, regardless of factors like statistical significance.
Other sources of bias relates to other study features that may introduce bias into a trial. This includes things like baseline imbalances, blocked randomization in unblinded trials, and study design characteristics.
Target Population
Sequence generation
Randomization
Allocation concealment
Intervention Group
Control Group
Blinding of participants/personnel
Exposed to Intervention
Not Exposed to Intervention
Blinding of outcome assessment
Outcome
Outcome
Incomplete outcome data
Follow-up
Follow-up
Selective outcome reporting
Reporting
Reporting
Thanks to our sponsors!

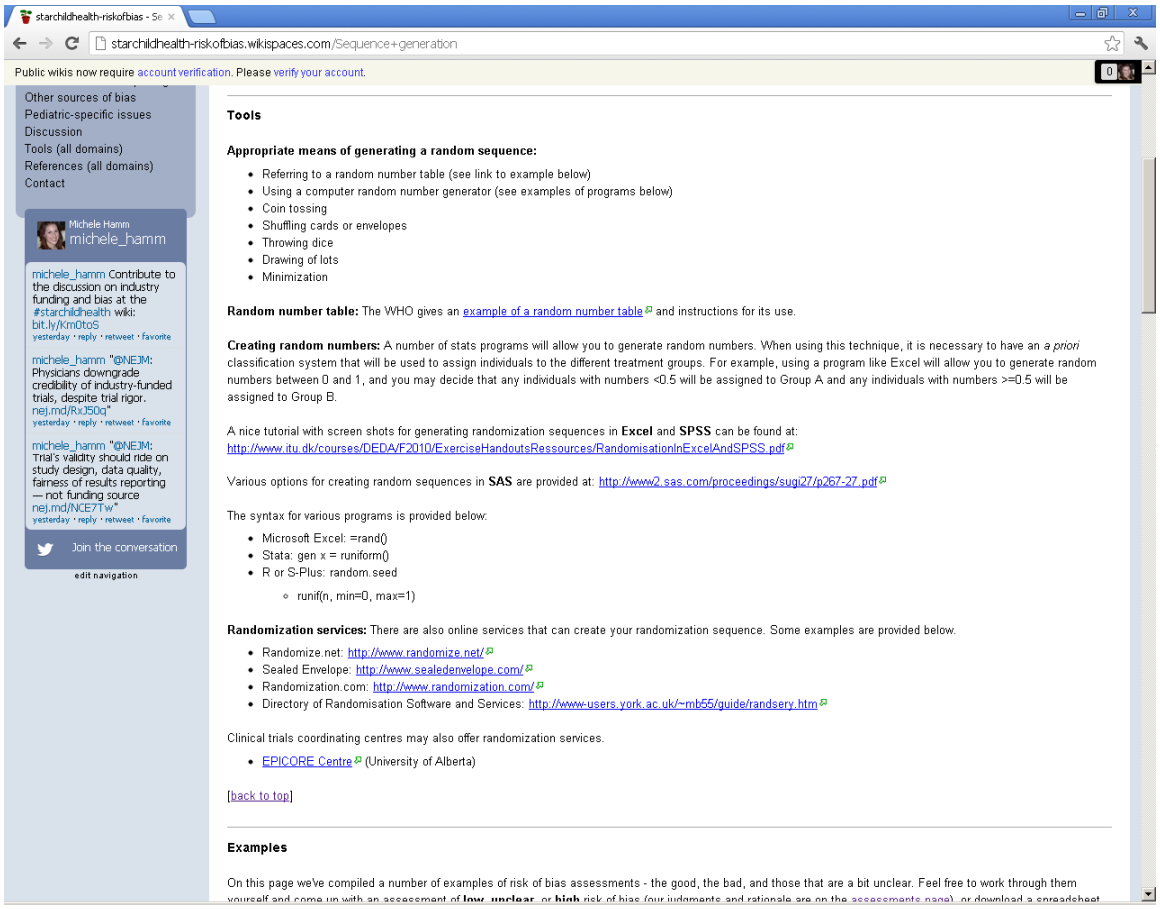
Home page


starchildhealth-riskofbias - ho
starchildhealth-riskofbias.wikispaces.com
Public wikis now require account verification. Please verify your account.
bias the results.
Selective outcome reporting is the reporting of a subset of the originally specified outcomes for the trial, leading to reporting bias. Two factors are important to consider: definition of the primary outcome, which should remain constant from the protocol to the publication, and inclusion of all outcomes in a report, regardless of factors like statistical significance.
Other sources of bias relates to other study features that may introduce bias into a trial. This includes things like baseline imbalances, blocked randomization in unblinded trials, and study design characteristics.
Thanks to our sponsors!
Knowledge Translation Canada
Application des Connaissances Canada
Presentation on risk of bias in pediatric randomized controlled trials, given at the 3rd StaR Child Health Summit in May 2012 in Winnipeg, Manitoba. Watch the video from the meeting here: http://bit.ly/KCQgVj
Risk of Bias_StaR Child Health Summit_07May12
Mind the Gap:
Risk of Bias in Pediatric Trials
StaR Child Health Summit
Winnipeg, Manitoba
May 7, 2012
Michele Hamm, MSc
Alberta Research Centre for Health Evidence
arche
toward knowledge
slideshare
Share
1 /34
View more PowerPoint from michele_hamm
Help · About · Blog · Pricing · Privacy · Terms · Support · Upgrade
Contributions to http://starchildhealth-riskofbias.wikispaces.com/ are licensed under a Creative Commons Attribution Share-Alike 3.0 License.
Portions not contributed by visitors are Copyright 2012 Tangient LLC.

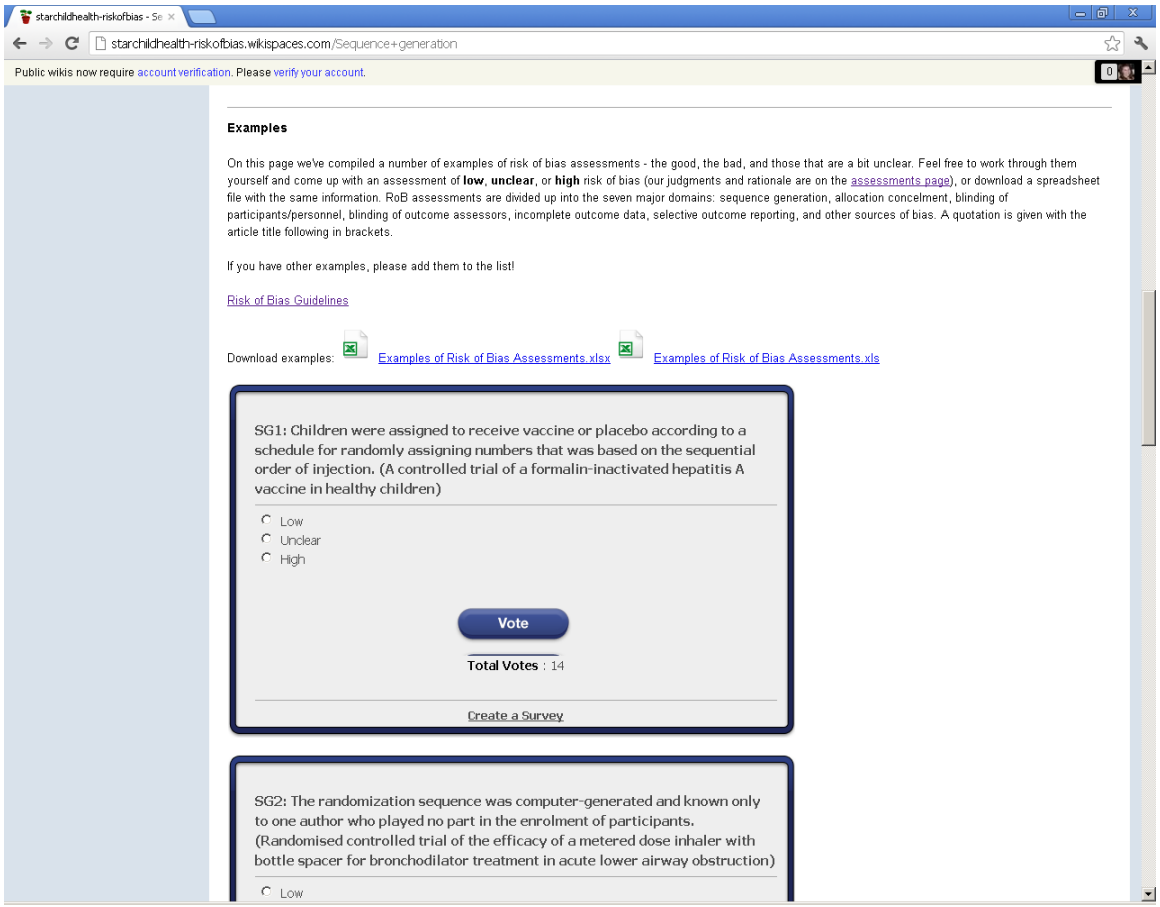
Home page



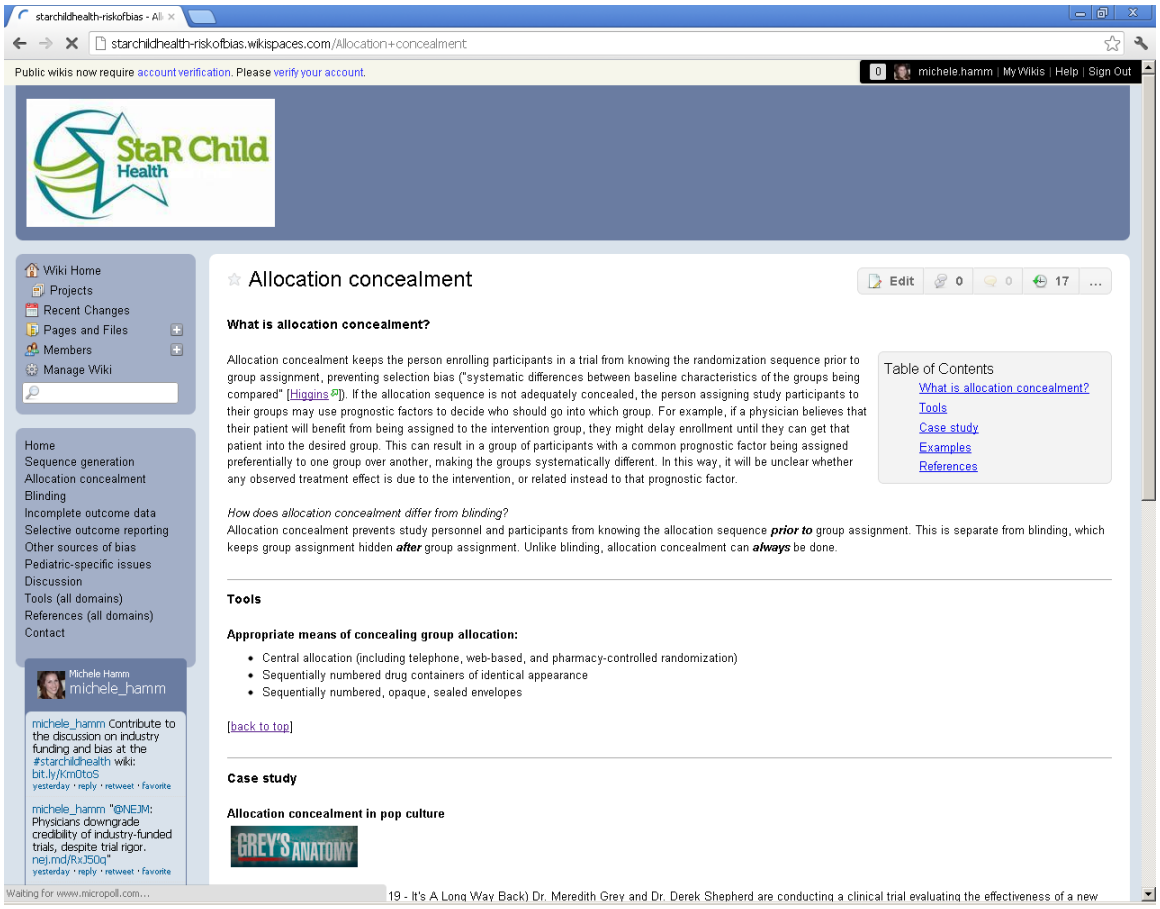
Sequence generation



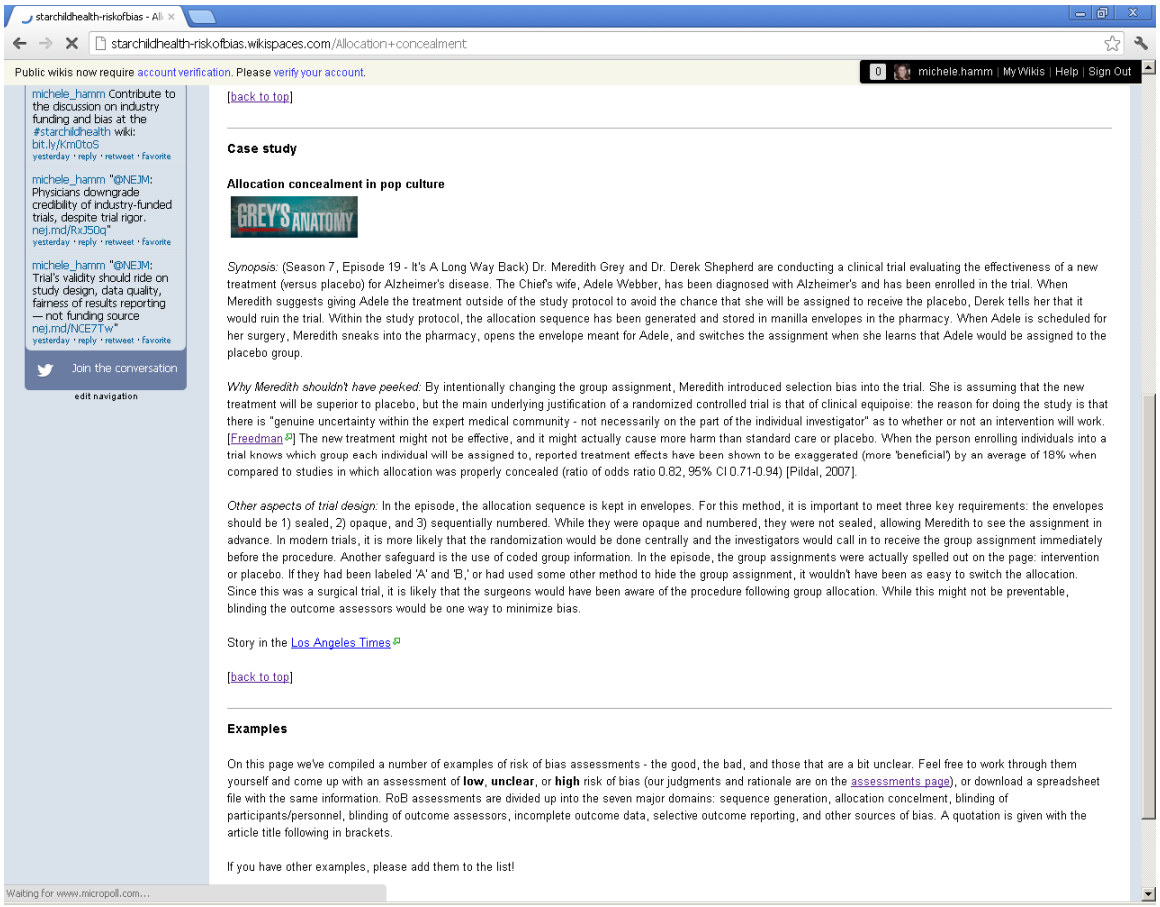
Sequence generation



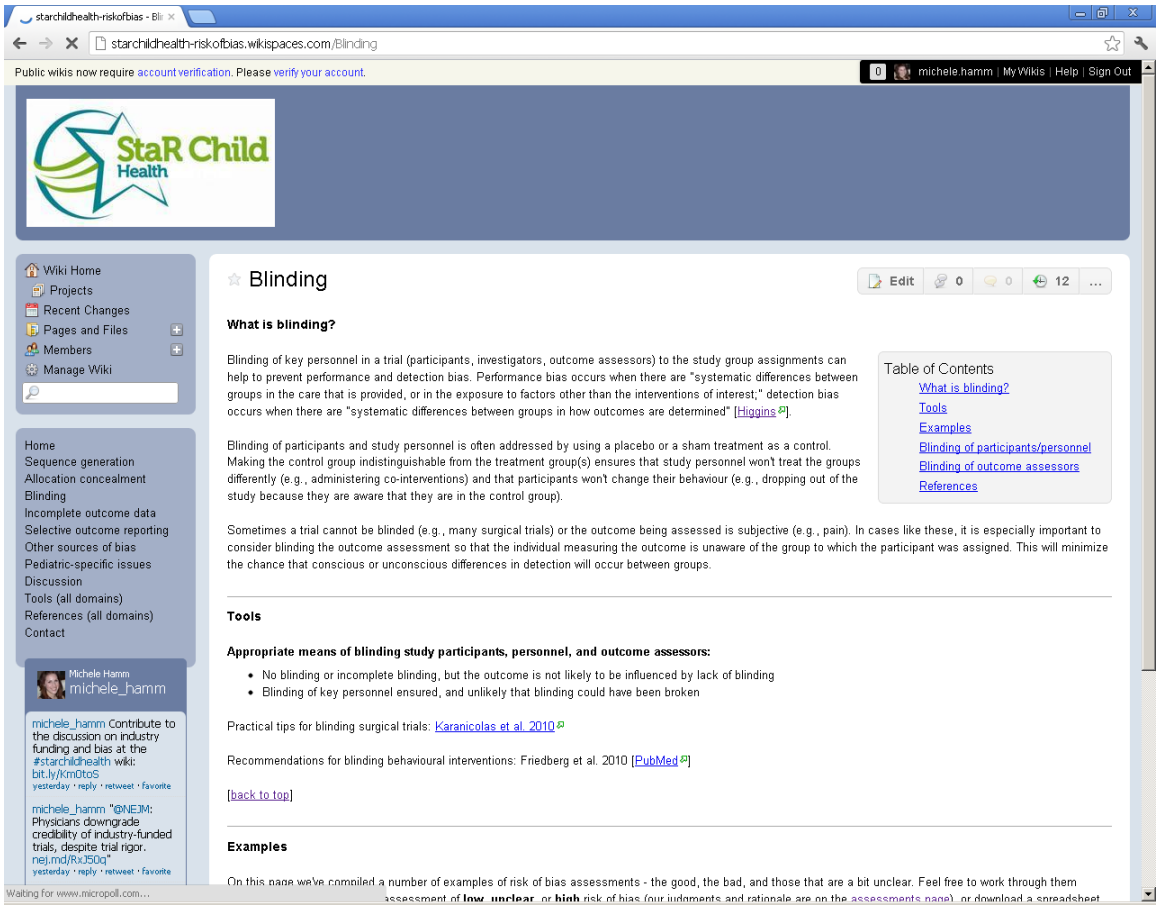
Sequence generation



Allocation concealment



Allocation concealment


starchildhealth-riskofbias - Bli
starchildhealth-riskofbias.wikispaces.com/Blinding
Public wikis now require account verification. Please verify your account.
michele.hamm | My Wikis | Help | Sign Out
StaR Child Health
Wiki Home
Projects
Recent Changes
Pages and Files
Members
Manage Wiki
Home
Sequence generation
Allocation concealment
Blinding
Incomplete outcome data
Selective outcome reporting
Other sources of bias
Pediatric-specific issues
Discussion
Tools (all domains)
References (all domains)
Contact
Michele Hamm
michele_hamm
michele_hamm Contribute to the discussion on industry funding and bias at the #starchildhealth wiki: bit.ly/KmOtoS
yesterday · reply · retweet · favorite
michele_hamm "@NEJM: Physicians downgrade credibility of industry-funded trials, despite trial rigor. nej.md/RxJ50q"
yesterday · reply · retweet · favorite
Blinding
Edit
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What is blinding?
Blinding of key personnel in a trial (participants, investigators, outcome assessors) to the study group assignments can help to prevent performance and detection bias. Performance bias occurs when there are "systematic differences between groups in the care that is provided, or in the exposure to factors other than the interventions of interest;" detection bias occurs when there are "systematic differences between groups in how outcomes are determined" [Higgins].
Blinding of participants and study personnel is often addressed by using a placebo or a sham treatment as a control. Making the control group indistinguishable from the treatment group(s) ensures that study personnel won't treat the groups differently (e.g., administering co-interventions) and that participants won't change their behaviour (e.g., dropping out of the study because they are aware that they are in the control group).
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Sometimes a trial cannot be blinded (e.g., many surgical trials) or the outcome being assessed is subjective (e.g., pain). In cases like these, it is especially important to consider blinding the outcome assessment so that the individual measuring the outcome is unaware of the group to which the participant was assigned. This will minimize the chance that conscious or unconscious differences in detection will occur between groups.
Tools
Appropriate means of blinding study participants, personnel, and outcome assessors:
No blinding or incomplete blinding, but the outcome is not likely to be influenced by lack of blinding
Blinding of key personnel ensured, and unlikely that blinding could have been broken
Practical tips for blinding surgical trials: Karanicolas et al. 2010
Recommendations for blinding behavioural interventions: Friedberg et al. 2010 [PubMed]
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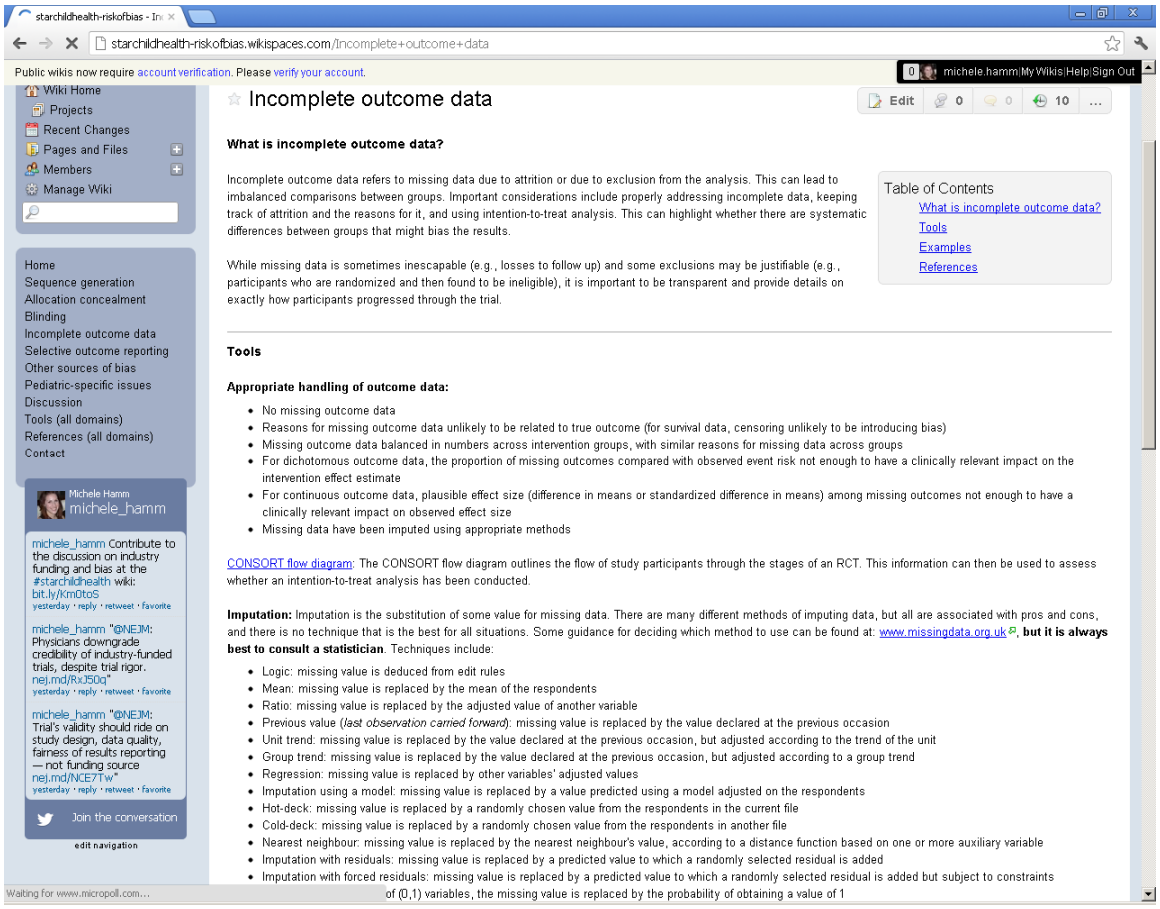
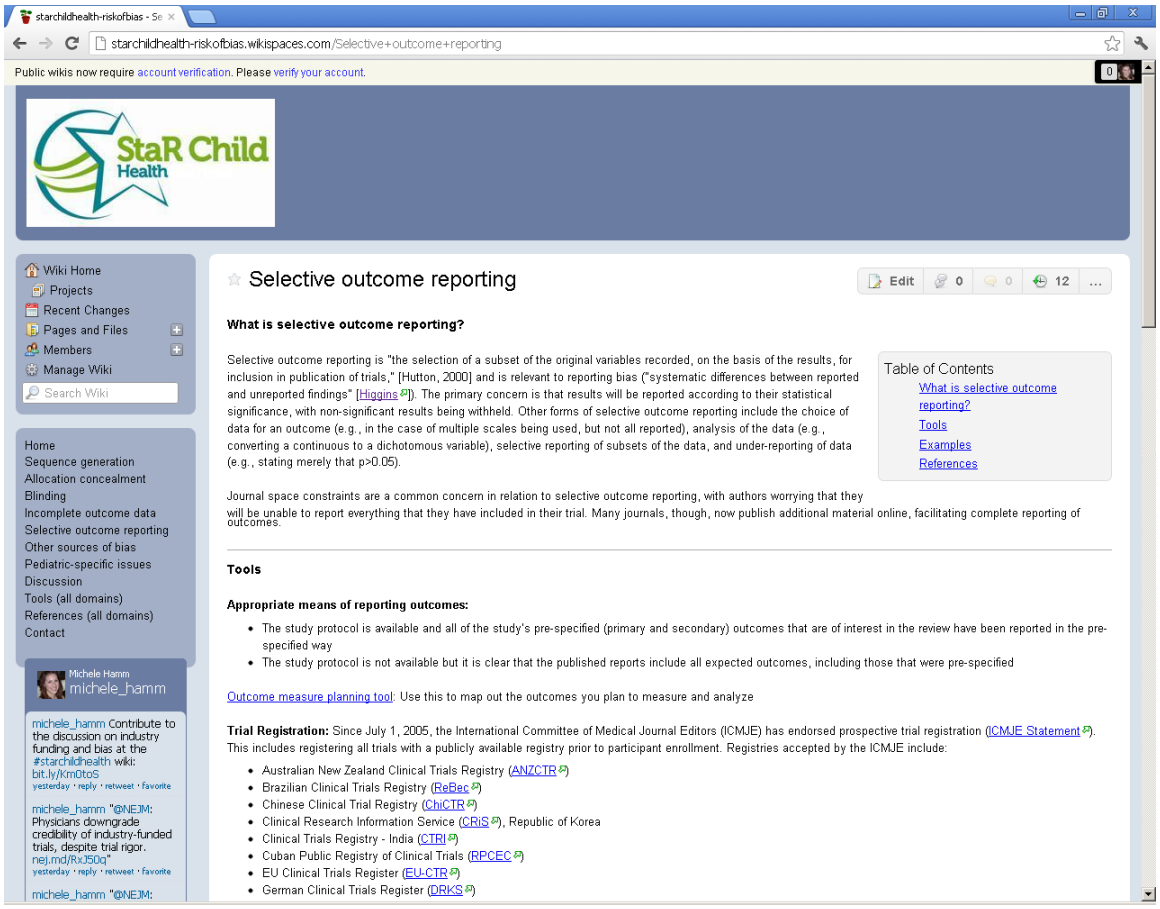
Examples
On this page we've compiled a number of examples of risk of bias assessments - the good, the bad, and those that are a bit unclear. Feel free to work through them
Waiting for www.micropoll.com...

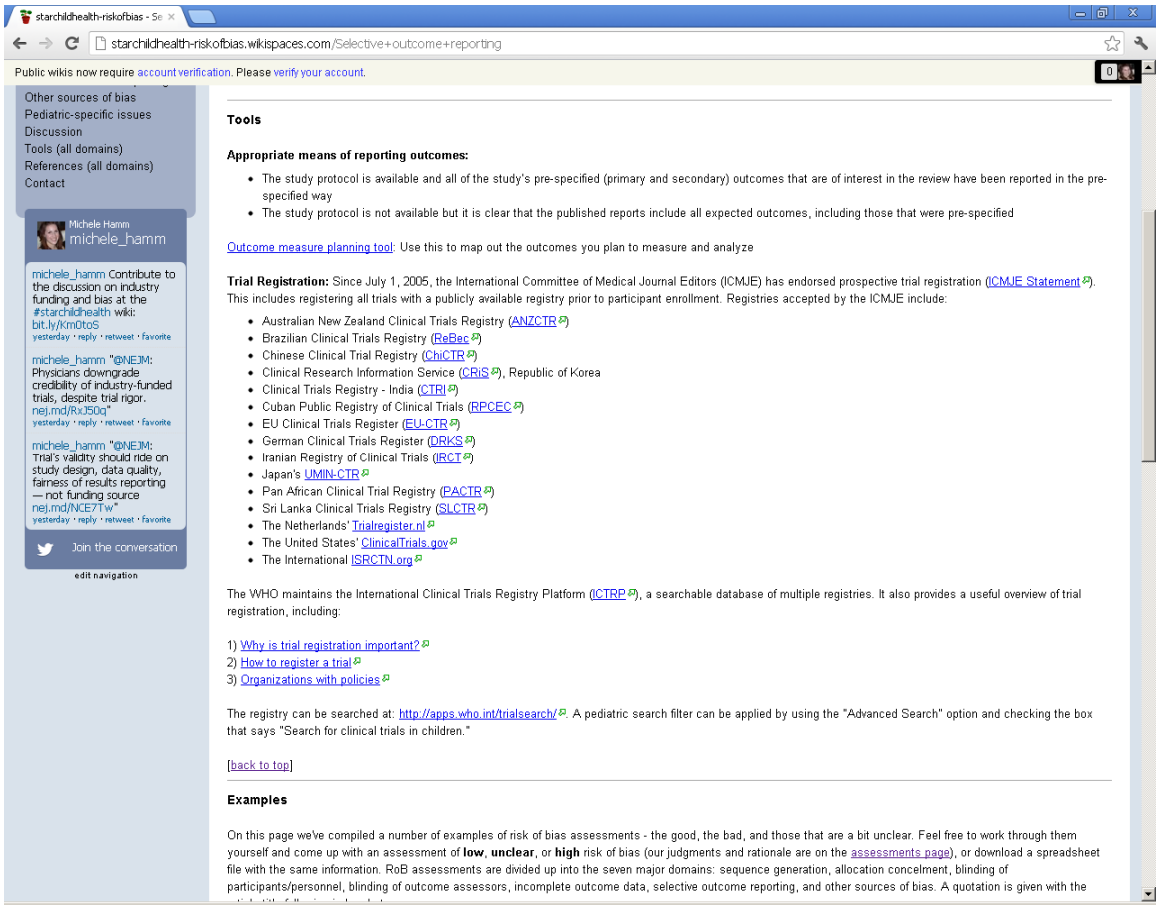
Blinding



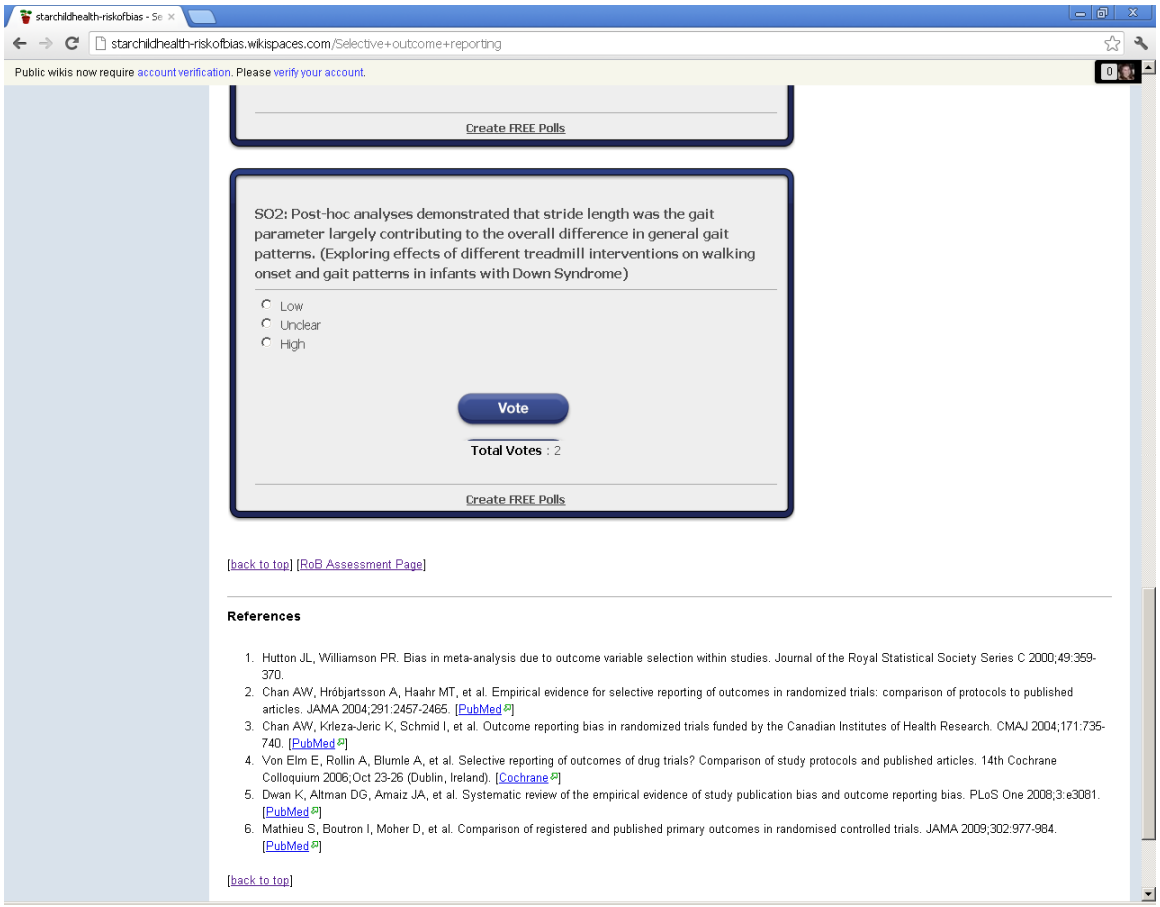
Incomplete outcome data



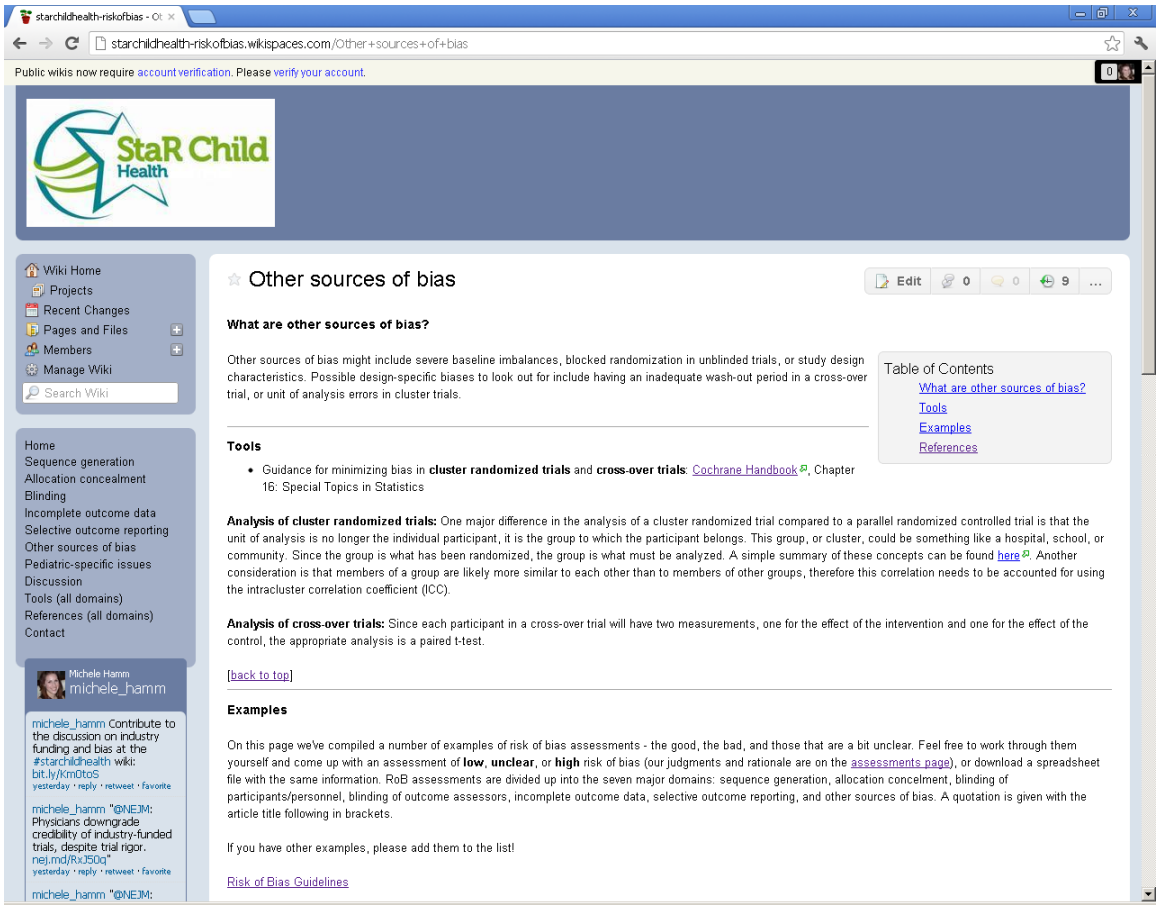
Selective outcome reporting



Selective outcome reporting

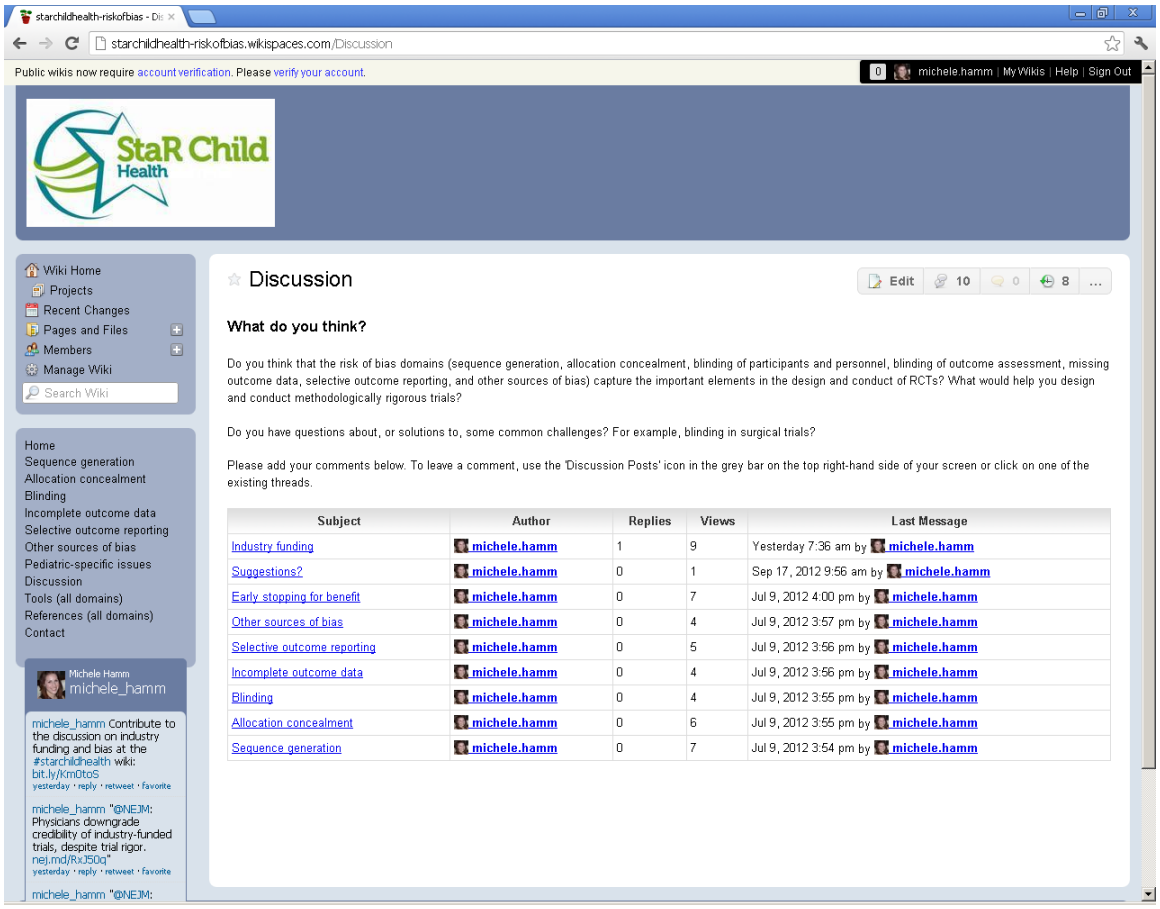


Selective outcome reporting



Other sources of bias

Pediatric-specific issues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Michele Hamm
michele_hamm
michele_hamm Contribute to the discussion on industry funding and bias at the #starchildhealth wiki: bit.ly/KmOtoS
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michele_hamm "@NEJM: Physicians downgrade credibility of industry-funded trials, despite trial rigor. nej.md/RxJ50q"
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Discussion
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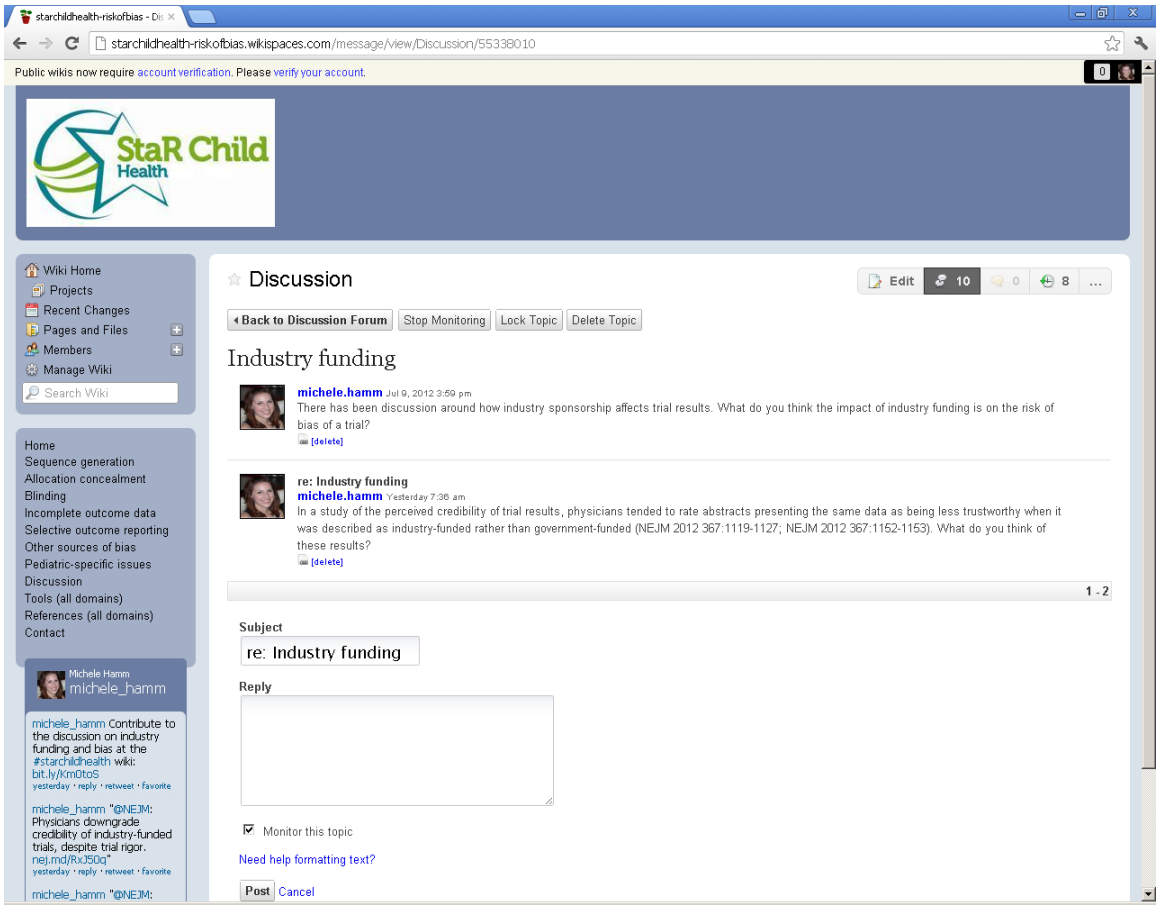
What do you think?
Do you think that the risk of bias domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, missing outcome data, selective outcome reporting, and other sources of bias) capture the important elements in the design and conduct of RCTs? What would help you design and conduct methodologically rigorous trials?
Do you have questions about, or solutions to, some common challenges? For example, blinding in surgical trials?
Please add your comments below. To leave a comment, use the 'Discussion Posts' icon in the grey bar on the top right-hand side of your screen or click on one of the existing threads.
Subject | Author | Replies | Views | Last Message
Industry funding | michele.hamm | 1 | 9 | Yesterday 7:36 am by michele.hamm
Suggestions? | michele.hamm | 0 | 1 | Sep 17, 2012 9:56 am by michele.hamm
Early stopping for benefit | michele.hamm | 0 | 7 | Jul 9, 2012 4:00 pm by michele.hamm
Other sources of bias | michele.hamm | 0 | 4 | Jul 9, 2012 3:57 pm by michele.hamm
Selective outcome reporting | michele.hamm | 0 | 5 | Jul 9, 2012 3:56 pm by michele.hamm
Incomplete outcome data | michele.hamm | 0 | 4 | Jul 9, 2012 3:56 pm by michele.hamm
Blinding | michele.hamm | 0 | 4 | Jul 9, 2012 3:55 pm by michele.hamm
Allocation concealment | michele.hamm | 0 | 6 | Jul 9, 2012 3:55 pm by michele.hamm
Sequence generation | michele.hamm | 0 | 7 | Jul 9, 2012 3:54 pm by michele.hamm

Discussion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michele_hamm "@NEJM:
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Stop Monitoring
Lock Topic
Delete Topic
Industry funding
michele.hamm Jul 9, 2012 3:59 pm
There has been discussion around how industry sponsorship affects trial results. What do you think the impact of industry funding is on the risk of bias of a trial?
[delete]
re: Industry funding
michele.hamm Yesterday 7:36 am
In a study of the perceived credibility of trial results, physicians tended to rate abstracts presenting the same data as being less trustworthy when it was described as industry-funded rather than government-funded (NEJM 2012 367:1119-1127; NEJM 2012 367:1152-1153). What do you think of these results?
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Subject
re: Industry funding
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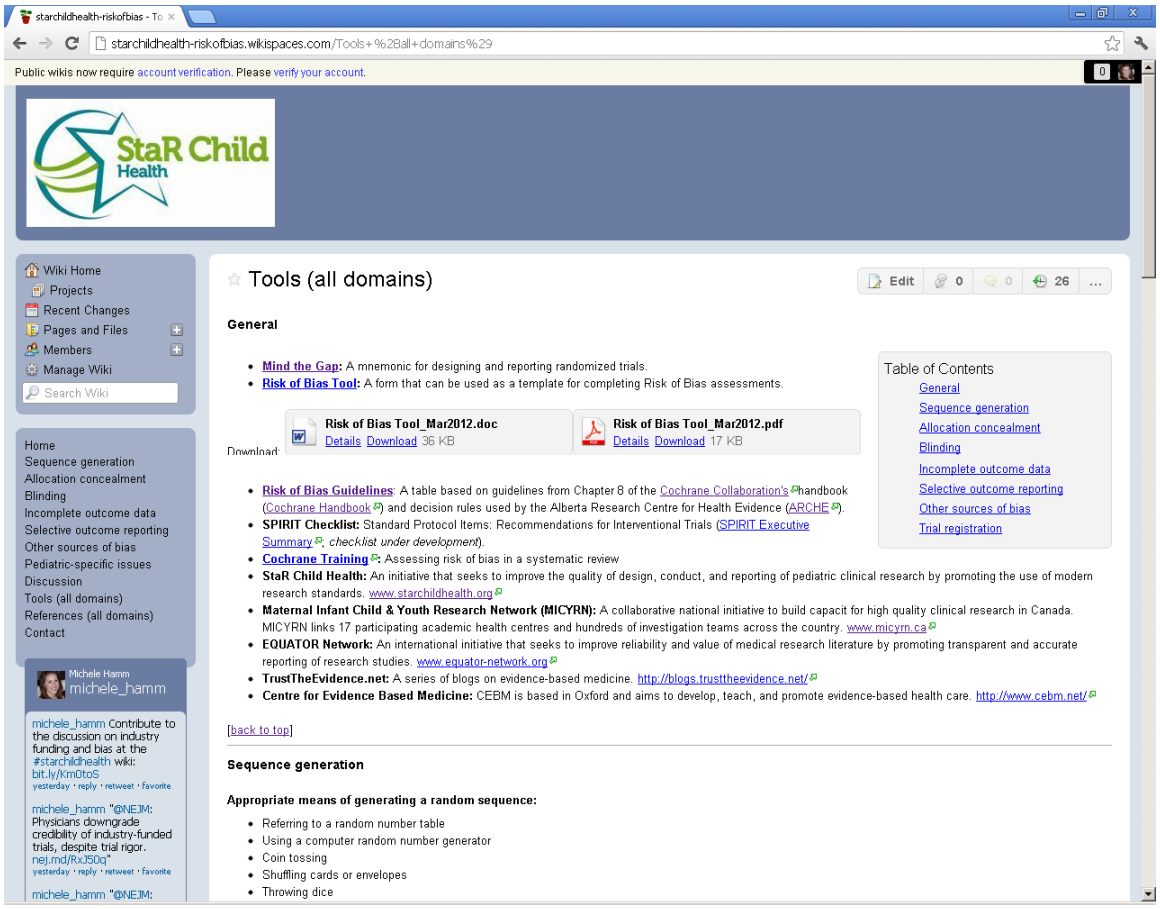
Discussion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General
Mind the Gap: A mnemonic for designing and reporting randomized trials.
Risk of Bias Tool: A form that can be used as a template for completing Risk of Bias assessments.
Download:
Risk of Bias Tool_Mar2012.doc
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Risk of Bias Tool_Mar2012.pdf
Details Download 17 KB
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Risk of Bias Guidelines: A table based on guidelines from Chapter 8 of the Cochrane Collaboration's handbook (Cochrane Handbook) and decision rules used by the Alberta Research Centre for Health Evidence (ARCHE).
SPIRIT Checklist: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT Executive Summary; checklist under development).
Cochrane Training: Assessing risk of bias in a systematic review
StaR Child Health: An initiative that seeks to improve the quality of design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards. www.starchildhealth.org
Maternal Infant Child & Youth Research Network (MICYRN): A collaborative national initiative to build capacit for high quality clinical research in Canada. MICYRN links 17 participating academic health centres and hundreds of investigation teams across the country. www.micyrn.ca
EQUATOR Network: An international initiative that seeks to improve reliability and value of medical research literature by promoting transparent and accurate reporting of research studies. www.equator-network.org
TrustTheEvidence.net: A series of blogs on evidence-based medicine. http://blogs.trusttheevidence.net/
Centre for Evidence Based Medicine: CEBM is based in Oxford and aims to develop, teach, and promote evidence-based health care. http://www.cebm.net/
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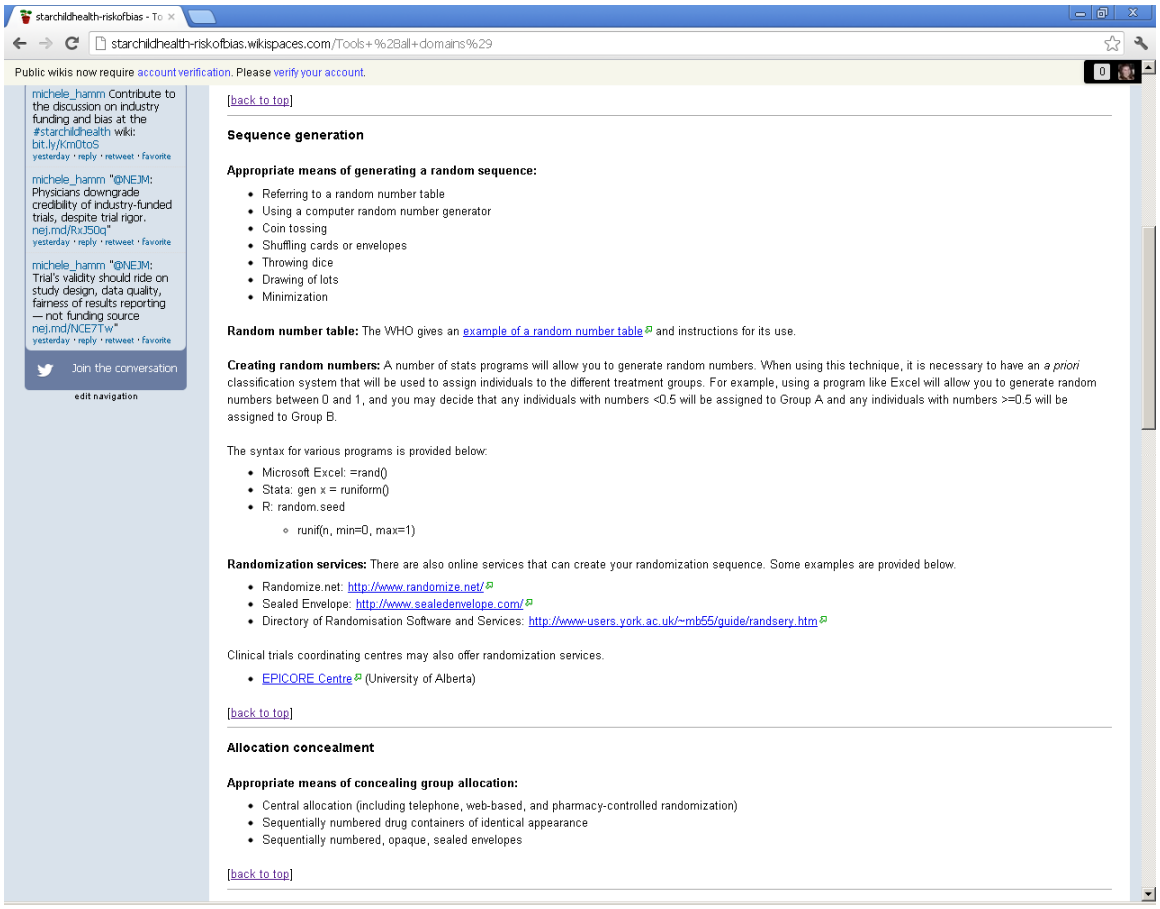
Sequence generation
Appropriate means of generating a random sequence:
Referring to a random number table
Using a computer random number generator
Coin tossing
Shuffling cards or envelopes
Throwing dice

Tools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Sequence generation
Appropriate means of generating a random sequence:
Referring to a random number table
Using a computer random number generator
Coin tossing
Shuffling cards or envelopes
Throwing dice
Drawing of lots
Minimization
Random number table: The WHO gives an example of a random number table and instructions for its use.
Creating random numbers: A number of stats programs will allow you to generate random numbers. When using this technique, it is necessary to have an a priori classification system that will be used to assign individuals to the different treatment groups. For example, using a program like Excel will allow you to generate random numbers between 0 and 1, and you may decide that any individuals with numbers <0.5 will be assigned to Group A and any individuals with numbers >=0.5 will be assigned to Group B.
The syntax for various programs is provided below:
Microsoft Excel: =rand()
Stata: gen x = runiform()
R: random.seed
runif(n, min=0, max=1)
Randomization services: There are also online services that can create your randomization sequence. Some examples are provided below.
Randomize.net: http://www.randomize.net/
Sealed Envelope: http://www.sealedenvelope.com/
Directory of Randomisation Software and Services: http://www-users.york.ac.uk/~mb55/guide/randsery.htm
Clinical trials coordinating centres may also offer randomization services.
EPICORE Centre (University of Alberta)
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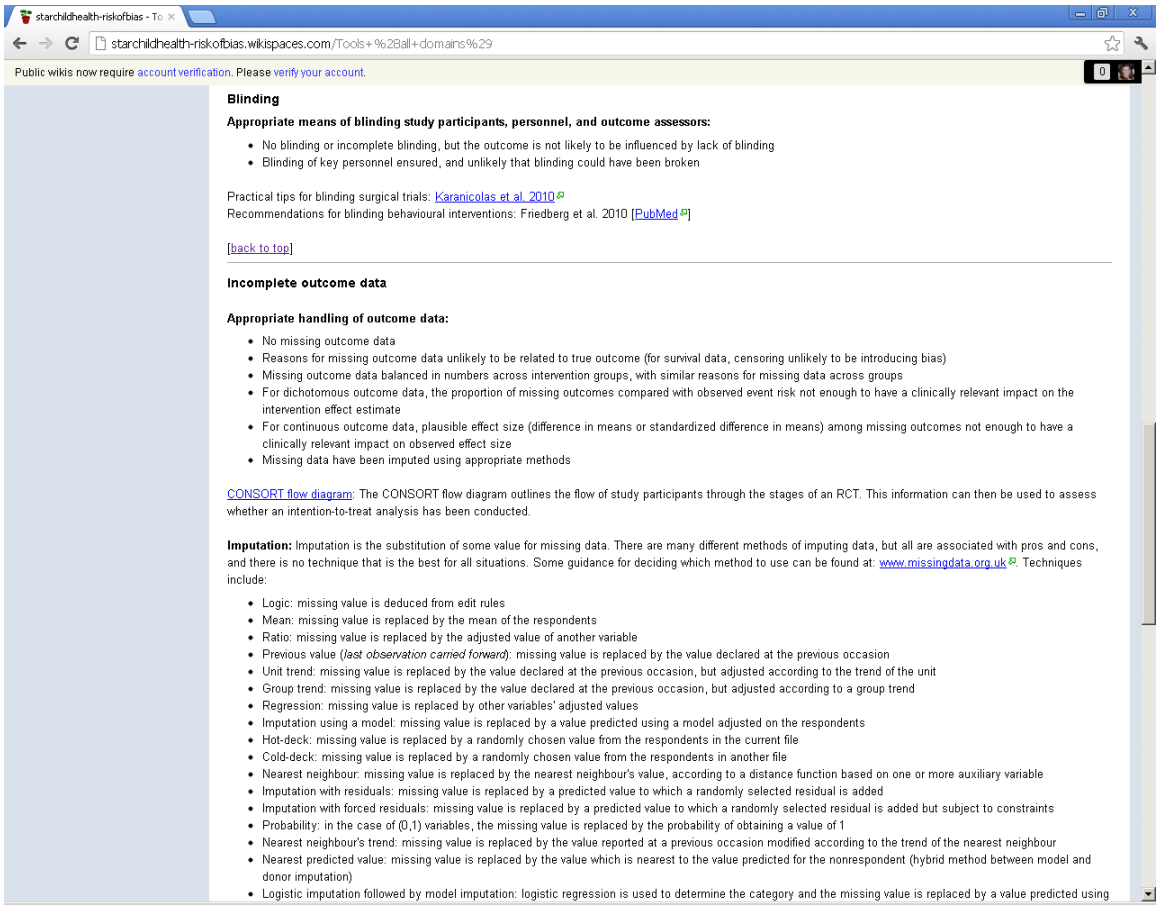
Allocation concealment
Appropriate means of concealing group allocation:
Central allocation (including telephone, web-based, and pharmacy-controlled randomization)
Sequentially numbered drug containers of identical appearance
Sequentially numbered, opaque, sealed envelopes
[back to top]

Tools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Blinding
Appropriate means of blinding study participants, personnel, and outcome assessors:
No blinding or incomplete blinding, but the outcome is not likely to be influenced by lack of blinding
Blinding of key personnel ensured, and unlikely that blinding could have been broken
Practical tips for blinding surgical trials: Karanicolas et al. 2010
Recommendations for blinding behavioural interventions: Friedberg et al. 2010 [PubMed]
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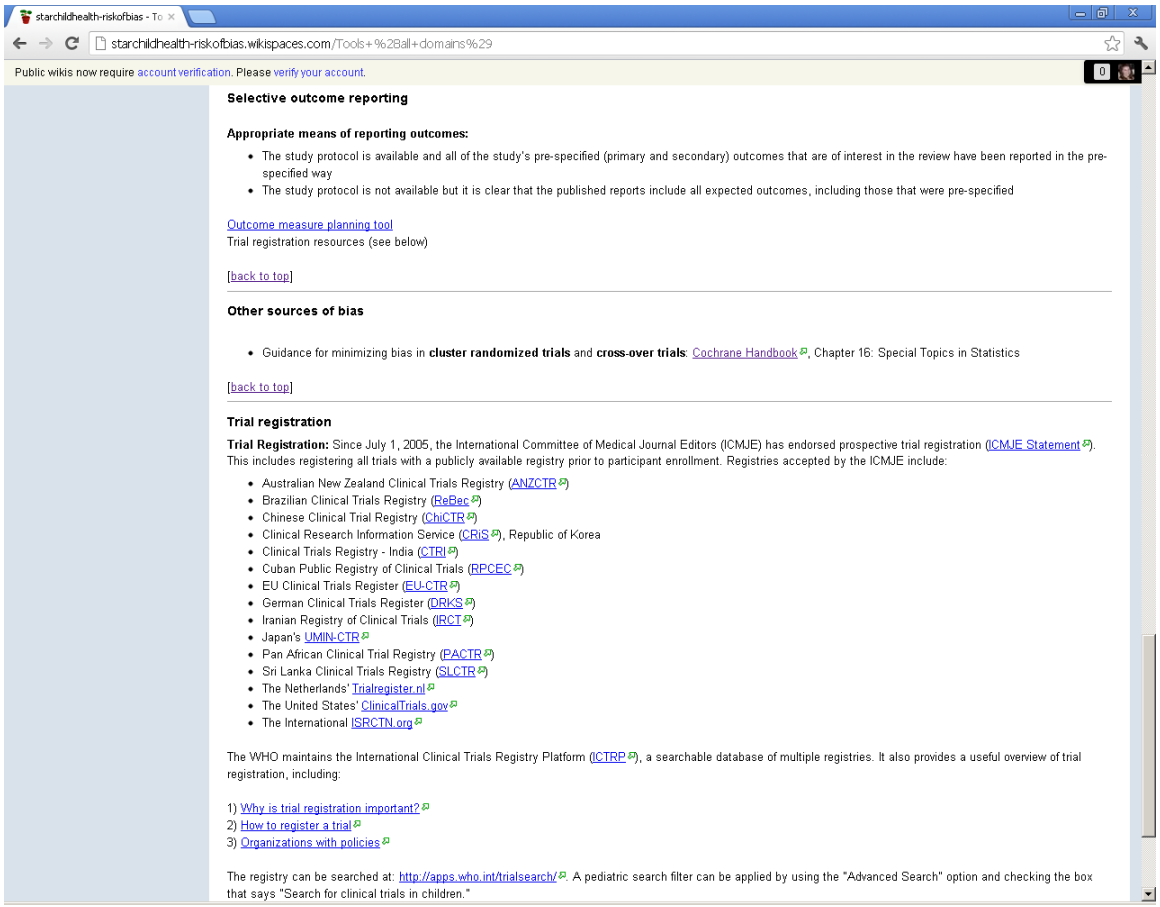
Incomplete outcome data
Appropriate handling of outcome data:
No missing outcome data
Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias)
Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate
For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size
Missing data have been imputed using appropriate methods
CONSORT flow diagram: The CONSORT flow diagram outlines the flow of study participants through the stages of an RCT. This information can then be used to assess whether an intention-to-treat analysis has been conducted.
Imputation: Imputation is the substitution of some value for missing data. There are many different methods of imputing data, but all are associated with pros and cons, and there is no technique that is the best for all situations. Some guidance for deciding which method to use can be found at: www.missingdata.org.uk. Techniques include:
Logic: missing value is deduced from edit rules
Mean: missing value is replaced by the mean of the respondents
Ratio: missing value is replaced by the adjusted value of another variable
Previous value (last observation carried forward): missing value is replaced by the value declared at the previous occasion
Unit trend: missing value is replaced by the value declared at the previous occasion, but adjusted according to the trend of the unit
Group trend: missing value is replaced by the value declared at the previous occasion, but adjusted according to a group trend
Regression: missing value is replaced by other variables' adjusted values
Imputation using a model: missing value is replaced by a value predicted using a model adjusted on the respondents
Hot-deck: missing value is replaced by a randomly chosen value from the respondents in the current file
Cold-deck: missing value is replaced by a randomly chosen value from the respondents in another file
Nearest neighbour: missing value is replaced by the nearest neighbour's value, according to a distance function based on one or more auxiliary variable
Imputation with residuals: missing value is replaced by a predicted value to which a randomly selected residual is added
Imputation with forced residuals: missing value is replaced by a predicted value to which a randomly selected residual is added but subject to constraints
Probability: in the case of (0,1) variables, the missing value is replaced by the probability of obtaining a value of 1
Nearest neighbour's trend: missing value is replaced by the value reported at a previous occasion modified according to the trend of the nearest neighbour
Nearest predicted value: missing value is replaced by the value which is nearest to the value predicted for the nonrespondent (hybrid method between model and donor imputation)
Logistic imputation followed by model imputation: logistic regression is used to determine the category and the missing value is replaced by a value predicted using

Tools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Selective outcome reporting
Appropriate means of reporting outcomes:
The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Outcome measure planning tool
Trial registration resources (see below)
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Other sources of bias
Guidance for minimizing bias in cluster randomized trials and cross-over trials: Cochrane Handbook, Chapter 16: Special Topics in Statistics
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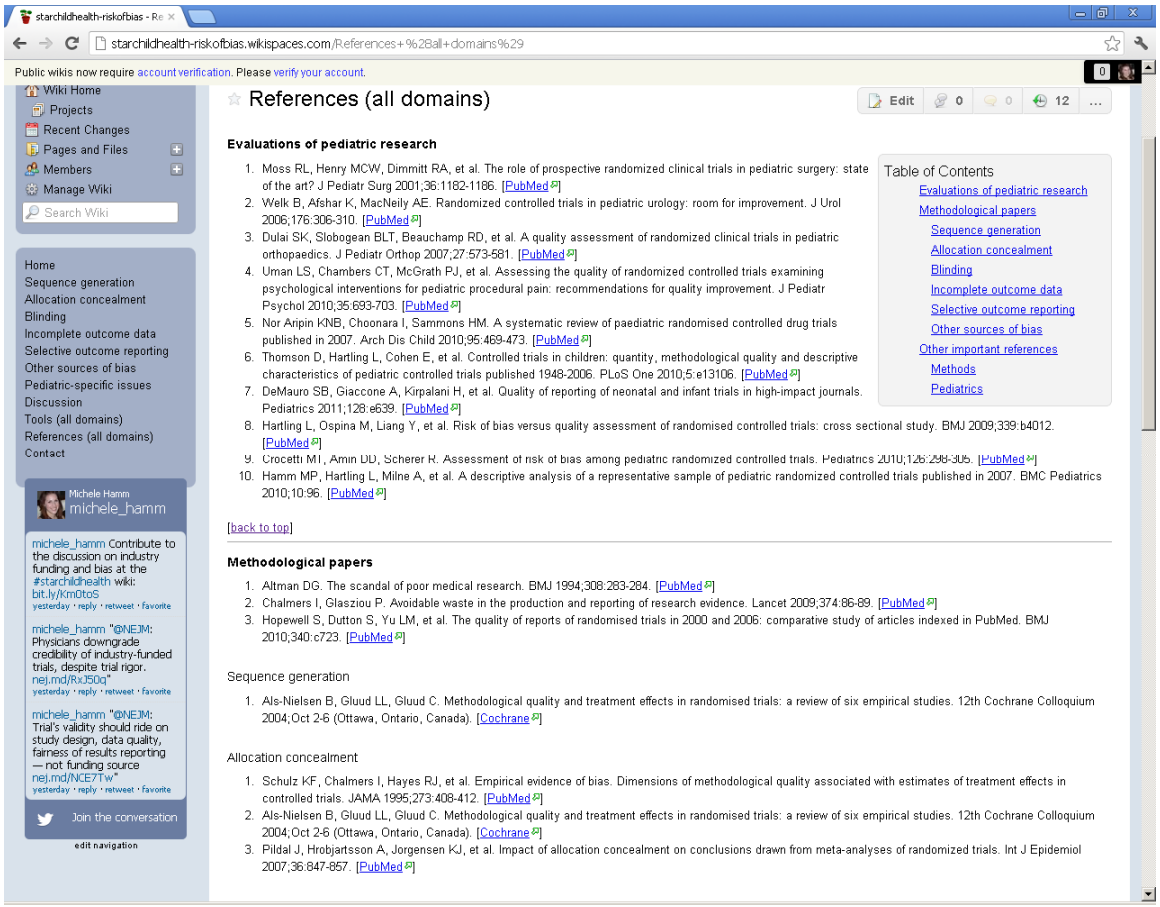
Trial registration
Trial Registration: Since July 1, 2005, the International Committee of Medical Journal Editors (ICMJE) has endorsed prospective trial registration (ICMJE Statement). This includes registering all trials with a publicly available registry prior to participant enrollment. Registries accepted by the ICMJE include:
Australian New Zealand Clinical Trials Registry (ANZCTR)
Brazilian Clinical Trials Registry (ReBec)
Chinese Clinical Trial Registry (ChiCTR)
Clinical Research Information Service (CRiS), Republic of Korea
Clinical Trials Registry - India (CTRI)
Cuban Public Registry of Clinical Trials (RPCEC)
EU Clinical Trials Register (EU-CTR)
German Clinical Trials Register (DRKS)
Iranian Registry of Clinical Trials (IRCT)
Japan's UMIN-CTR
Pan African Clinical Trial Registry (PACTR)
Sri Lanka Clinical Trials Registry (SLCTR)
The Netherlands' Trialregister.nl
The United States' ClinicalTrials.gov
The International ISRCTN.org
The WHO maintains the International Clinical Trials Registry Platform (ICTRP), a searchable database of multiple registries. It also provides a useful overview of trial registration, including:
1) Why is trial registration important?
2) How to register a trial
3) Organizations with policies
The registry can be searched at: http://apps.who.int/trialsearch/. A pediatric search filter can be applied by using the "Advanced Search" option and checking the box that says "Search for clinical trials in children."

Tools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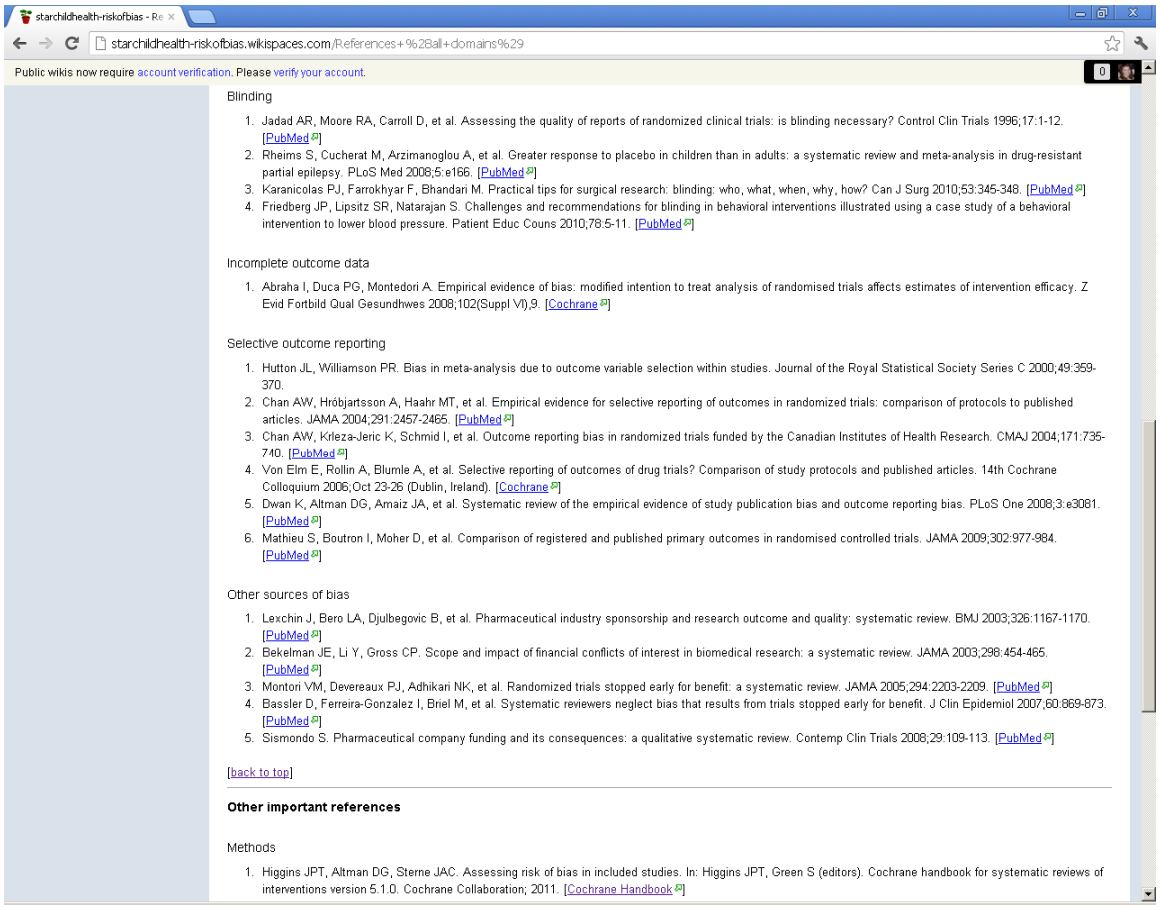
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Appendix U. EPOC framework: knowledge translation interventions for risk of bias

Intervention type	Relevant theories	Intervention options		Survey and interview findings
Distribution of educational materials		*Static website*		
	-Diffusion of Innovations -Theory of Planned Behaviour	Pros: -Farmer, 2008: compared to no intervention, printed educational materials may have benefits on process outcomes (4.3% absolute improvement in categorical outcomes, 13.6% in continuous outcomes)	Cons: -requires time and initiative on the part of the user -only appeals to users looking for reference materials	-62.0% of survey respondents agreed that educational materials would be useful (ranked 5th out of 5) -online resources were mentioned favourably by two interview respondents
		Wiki		
	-Diffusion of Innovations -Social Influences Theory -Theory of Planned Behaviour	Pros: -as above for a static website -versatility of modes of presenting content – can be both static and dynamic -interactivity is novel and may increase adoption/knowledge -precedent has been set for using wikis to disseminate methods research (whatiskt.wikispaces.com; crtethics.wikispaces.com); however, still fairly novel -Forsetlund, 2009: mixed interactive and didactic meetings were more effective than didactic or interactive meetings alone	Cons: -requires time and initiative on the part of the user -may be a lack of interest to contributing -site needs to be monitored/ maintained	-90.7% and 88.7% of survey respondents agreed that checklists/ reminders and online resources, respectively, would be useful (ranked 1st and 2nd out of 5) -checklists, opinion leaders, and educational materials could be incorporated into this format -elements that could be incorporated into a wiki were mentioned 13 times by interview respondents (checklists, online resources, contact list, endorsement, flow diagram)

		-Akl, 2008: educational games increased scores on knowledge test -potential for interprofessional education (researchers from different disciplines, e.g., epi vs. clinical focus); Reeves, 2008: 4/6 studies on interprofessional education found improvements in some ways that professionals worked together		
		Mobile app		
	-Diffusion of Innovations -Theory of Planned Behaviour	Pros: -convenient	Cons: -information likely too detailed to access on the go – researchers writing a protocol will likely be at their computers	N/A
Educational meetings		Combined with Distribution of educational materials.		
Educational outreach visits		Not relevant.		
Local consensus processes		Not relevant.		
Local opinion leaders	-Diffusion of Innovations -Social Influences Theory -Theory of	Pros: -endorsement, encouragement can be incorporated into social media strategies (e.g., *wiki*) -Flodgren, 2011: 12% median absolute increase in compliance	Cons: -requires effort on the part of busy people	-73.2% of survey respondents agreed that local opinion leaders would be useful (ranked 4th out of 5)

	Planned Behaviour	in behaviour		
Patient-mediated interventions		Not relevant.		
Audit and feedback		*Protocol review + feedback*		
	-Theory of Planned Behaviour	Pros: -directly relevant to individual researchers -linked to an activity already being conducted (i.e., no extra work required) -Jamtvedt, 2006: 5% median absolute change in clinical behaviour vs. no intervention; IQR: 3-11%	Cons: -very resource-intensive	-protocol review was mentioned favourably by 3 interview respondents
Reminders		*Email reminders/listservs*		
	-Theory of Planned Behaviour	Pros: -Shojania, 2009: on-screen, point-of-care reminders improved process adherence 4.2% (IQR 0.4-18.8%)	Cons: -email overload -may overlook helpful information if it is not sent at a time when it is specifically relevant	-90.7% of survey respondents agreed that reminders/checklists would be useful (ranked 1st out of 5)
Marketing		Not relevant.		
Mass media		*Social media – Facebook, Twitter, YouTube*		
	-Social Capital Theory -Social Network Theory	Pros: -social media is now becoming a widely used format for information-seeking -would potentially make a good adjunct	Cons: -very specific (/small) target audience – likely that any return would not be worth the necessary investment of resources -Grilli, 2002: unclear on whether	N/A

	coverage brings about appropriate change in target groups

**While the EPOC reviews are based on changing clinician behaviour, this evidence provides a base from which interventions targeting researcher behaviour can be developed and evaluated*

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