How to Incorporate Non-Randomized Studies in Cochrane Reviews of Patient Safety

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Scientific Evidence for Healthcare Quality and Patient Safety

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University of Ottawa

13 Including non-randomized studies

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Cochrane Handbook for
**Systematic Reviews
of Interventions**

Editors   JULIAN P. T. HIGGINS | SALLY GREEN

COCHRANE BOOK SERIES

WILEY-BLACKWELL

Information/Education

1. Gordon M, Findley R., Educational interventions to improve handover in health care: a systematic review. Med Educ. 2011 Nov;45(11):1081-9.

2. McCulloch P, Rathbone J, Catchpole K., Interventions to improve teamwork and communications among healthcare staff. Br J Surg. 2011 Apr;98(4):469-79.

3. Rabøl LI, Østergaard D, Mogensen T., Outcomes of classroom-based team training interventions for multiprofessional hospital staff. A systematic review. Qual Saf Health Care. 2010 Dec;19(6):e27.

4. Fischer SH, Tjia J, Field TS., Impact of health information technology interventions to improve medication laboratory monitoring for ambulatory patients: a systematic review. J Am Med Inform Assoc. 2010 Nov-Dec;17(6):631-6.

5. Nagpal K, Vats A, Lamb B, Ashrafian H, Sevdalis N, Vincent C, Moorthy K., Information transfer and communication in surgery: a systematic review. Ann Surg. 2010 Aug; 252(2):225-39.

6. Kilner E, Sheppard LA., The role of teamwork and communication in the emergency department: a systematic review. Int Emerg Nurs. 2010 Jul; 18(3):127-37.

7. Merién AE, van de Ven J, Mol BW, Houterman S, Oei SG. Multidisciplinary team training in a simulation setting for acute obstetric emergencies: a systematic review.Obstet Gynecol. 2010 May;115(5):1021-31.

Gordon 2011 - Handover

Educational interventions to improve handover in health care: a systematic review
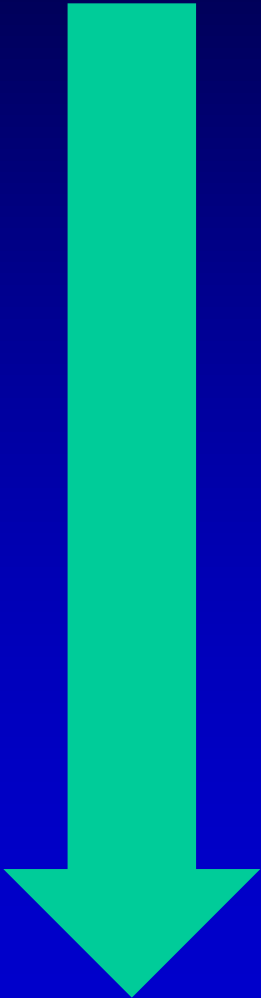
Morris Gordon[1,2] & Rebecca Findley[2]

- **Handover is the accurate, reliable communication of task-relevant information on patients across shift changes in staff**

- **Communication failure at handover is identified as a major source of error within patient care (patient safety)**

- **Research has found dissatisfaction amongst junior staff with current practices as a result of the lack of policies and training**

Objective: **To determine the characteristics of educational interventions employed to enhance handover amongst health professionals and to establish the effectiveness of these interventions**

Systematic Review

Steps of a Systematic Review

- **Clearly formulated question**

- **Comprehensive data search**

- **Unbiased selection and extraction process**

- **Critical appraisal**

- **Analysis/synthesis of data**
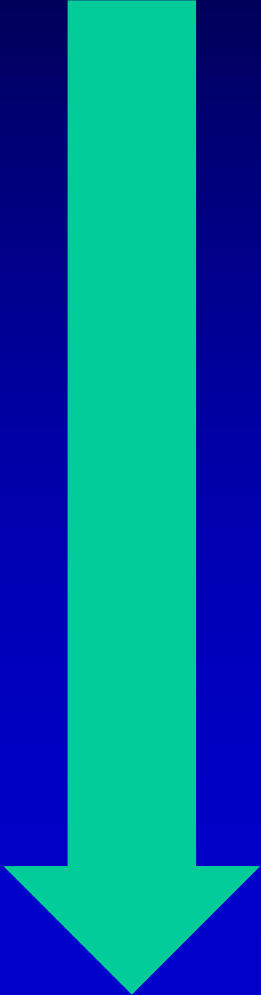
- **Interpretation of results**

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Gordon 2011 – Handover
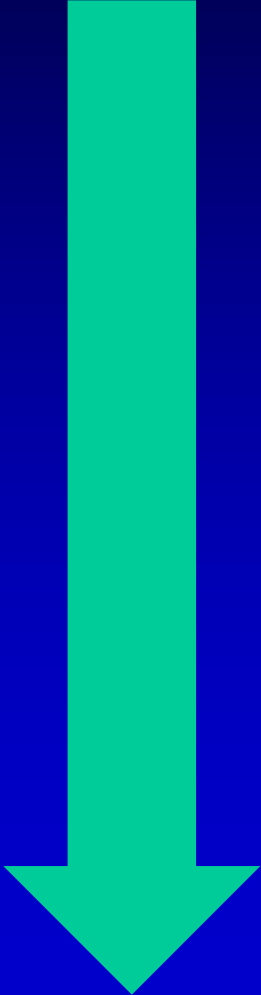## *Clearly formulated question*

PICO

Population	**Medical and nursing staff, including undergraduates in in-patient medical establishments**
Intervention	**Any structured educational activity**
Comparison	**Standard/usual strategy (not explicitly identified)**
Outcome	**Kirkpatrick's adapted hierarchy; 4 levels of outcome** **Level 1 - reaction to intervention** **Level 2a - attitudes and confidence** **Level 2b - knowledge and skills** **Level 3 - behaviour change** **Level 4 - patient outcomes (includes patient safety)**

Types of studies

- **All interventional study designs were considered for this review**
  - **commentaries, surveys, audits, review articles not included**

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Comprehensive data search

Some points to remember …

Exhaustive searching, which is recommended for RCT, may not be justified when reviewing NRS

Do not limit search strategies by index terms for study design

- **Not easy to design a restrictive search strategy for particular NRS since filters and indexing fields to limit searches unlikely helpful (NRS design labels not used consistently in studies, NRS not indexed reliably by bibliographic databases)**

Do not limit search strategies to specific outcomes

- **When searching NRS for specific rare or long-term outcomes, including free text and MeSH terms for specific outcomes in the search strategy may be justified**

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Comprehensive Data Search

Online databases searched (standardized search strategy)

- **MEDLINE**
- **EMBASE**
- **CINAHL (Cumulative Index to Nursing and Allied Health Literature)**
- **British Nursing Index (BNI)**
- **PsycINFO**
- **ERIC (Educational Resource Information Centre)**
- **British Education Index (BEI)**
- **Cochrane Trials Database**
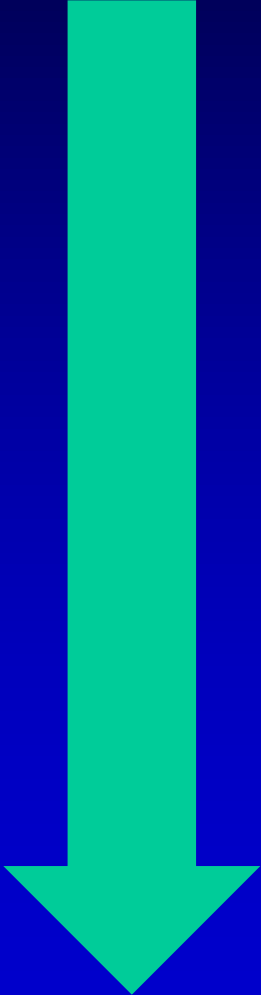
Reference lists from included studies were searched for further relevant studies

Online abstracts from relevant education societies, including:

- **Association for the Study of Medical Education**
- **Association for Medical Education in Europe**

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Unbiased selection and extraction

Some points to remember …

Judging eligibility: Reviewing citations and abstracts identified by searching will be very time consuming since

- Large volume of citations identified
- Needed information for eligibility may not be in title or abstract

Data collection: In addition to data required for SR of RCT, need:

- Confounding factors considered
- Group comparability on confounding factors and control methods
- Aspects of risk of bias specific for NRS
- Adjusted and unadjusted effect estimates

Adjusted results: For NRS, comparisons of the raw data are 'unadjusted' and susceptible to confounding; need adjusted

- Can display adjusted estimates in forest plots and pool estimates using generic inverse variance method , if appropriate

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Unbiased Selection and Extraction Process

- Citations reviewed independently by each of review authors

- Agreement between review authors assessed using Cohen's kappa statistic

- Potentially relevant abstracts independently reviewed using a screening checklist and full papers obtained for any studies that appeared to meet the inclusion criteria

- Disputes resolved by consensus

- Full manuscripts for included studies assessed independently by each review author

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Comprehensive Search/Selection - Results
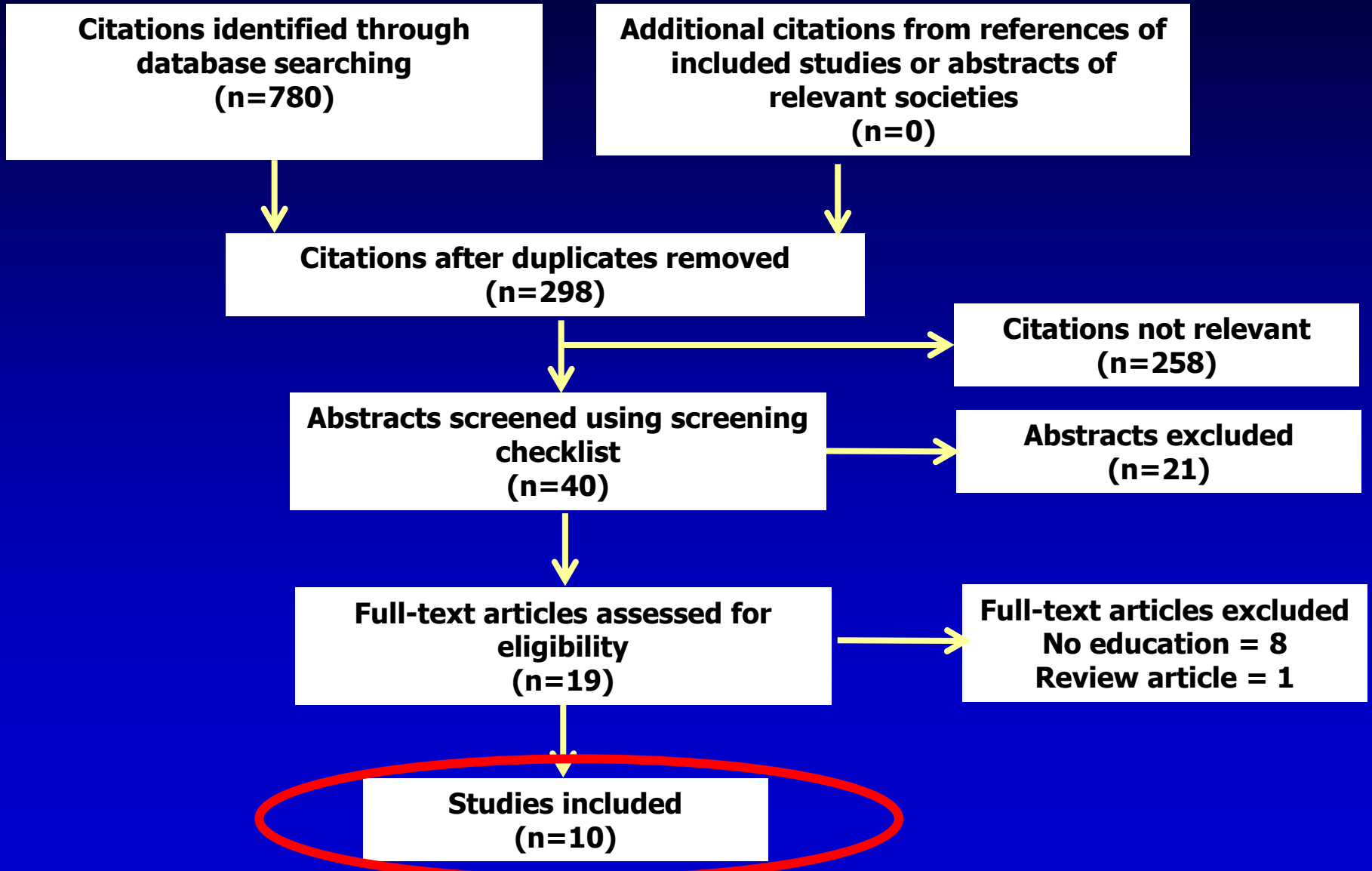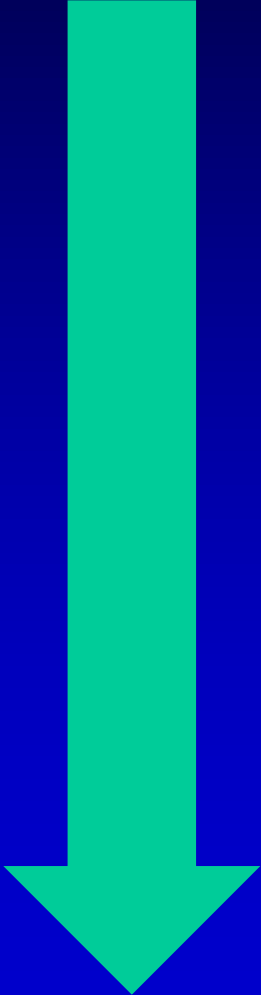
Systematic Review

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Critical appraisal - risk of bias

Some points to remember …

Reporting guideline STROBE only recently developed

Often no protocol for NRS review; protocol protect against bias
- **At the protocol stage, compile a list of potential confounding factors and justify the choice, independent of studies**
- **At the protocol stage, determine how ROB in primary studies assessed**

Assessing ROB: Difficult to develop a generic tool for evaluating ROB for NRS since different NRS designs have varying susceptibility to different biases
- **Several tools for assessment of risk of bias may be needed**
- **Methodological information needed for ROB can be difficult to find**

Sources of Bias: As for RCT, dimensions of bias assessed for NRS include: selection, performance, detection, attrition, reporting
- **NRS unconcealed allocation means groups likely not comparable (selection bias)**

Critical appraisal - risk of bias

Some more points to remember ...

Selection Bias/Confounding: **When selection bias produces imbalances in prognostic factors associated with the outcome then 'confounding' occurs**

- **Statistical methods sometimes used to counter confounding by producing 'adjusted' estimates**
- **Assessment of study quality may involve making judgments about the appropriateness of this analysis**

Confounding factors: **For potentials confounding factors:**

- **list in protocol**
- **identify those included/excluded in NRS**
- **identify ways measured**
- **assess balance between groups at baseline**
- **identify ways controlled (match, stratify, model; propensity)**
- **Residual confounding**
- **Confounding by indication**

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Critical Appraisal

Quality of the studies - used 16 quality-based criteria by Reed, *Ann Intern Med* **2005**

	16 Criteria
	Literature review described
	Clear objectives reported
	Appropriate design
	Study design reported
	Comparison group used
	Any randomisation
	Blinding
	Learner characteristics
	Could the study be replicated
	Resources described
	Outcomes match objectives
	Replicable data collection
	Statistical tests used
	If used, are they appropriate
	Outcomes
	Strength of conclusions

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Critical Appraisal

Strength of the conclusions drawn by each study was rated on a numeric scale, in line with Best Evidence Medical Education (BEME) guidance

- **Measure of how well conclusions made are supported by data presented**
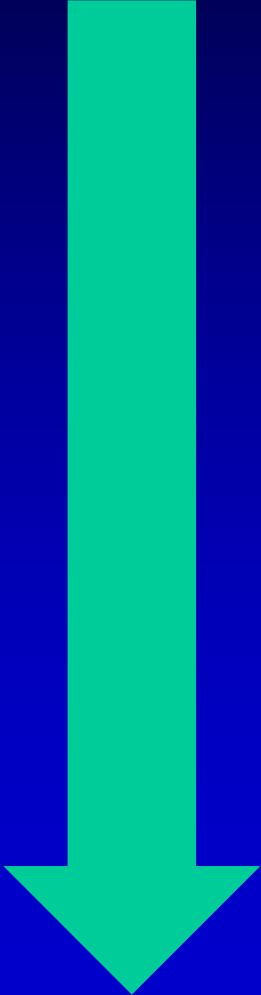
- **Disputes resolved by discussion until consensus**

Results and strength of conclusions

1 – No clear conclusions can be drawn. Not significant
2 – Results ambiguous, but there appears to be a trend.
3 – Conclusions can probably be based on the results.
4 – Results are clear and very likely to be true.
5 – Results are unequivocal.

Systematic Review

Steps of a Systematic Review

- Clearly formulated question

- Comprehensive data search

- Unbiased selection and extraction process

- Critical appraisal

- **Analysis/synthesis of data**

- Interpretation of results

Analysis/Synthesis of Data

Some point to remember ...

What is different when including NRS?

- **Expect greater heterogeneity than for a SR of RCT due to the increased potential for methodological diversity**

- **Usually appropriate to analyze adjusted effect estimates (i.e. analyses attempting to 'control for confounding')**

- **Danger is that a large NRS of poor methodological quality (for example based on routinely collected data) may dominate the findings of other smaller studies at less risk of bias**

Analysis/Synthesis of Data

Some more point to remember …

When pooling judged not appropriate

- **Studies not sufficiently homogeneous to combine then display study results in a forest plot but suppress pooled estimate**

- **Can sort studies in the forest plot by feature believed to reflect susceptibility to bias**

- **Heterogeneity diagnostics and investigations are worthwhile even when a judgment made that a pooled effect estimate is not**

- **Narrative syntheses problematic since difficult to describe results without being selective or emphasizing some findings over others; ideally, set out in protocol**

- **Recommend that NRS of different study designs should not be pooled (different designs influenced to varying degrees by different sources of bias; different designs should expected to differ increasing heterogeneity)**

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Analysis/Synthesis of Data - Results

Types of studies:
- **6 before-after study**
- **3 action-based study**
- **1 non-randomized controlled study**

Interventions – wide range
- **workshops**
- **periodic lectures**
- **small group discussions**
- **audit and feedback**
- **online/printed material**
etc

Outcome measures – wide range
- **quality checklist/scores**
- **survey – KAB**
- **questionnaires – opinions**
etc

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Analysis/Synthesis of Data - Results

Levels of Outcomes
- 6 level 2a (attitudes and confidence)
- 3 level 2b (knowledge and skills)
- 1 level 3 (behaviour change)

Strength of Conclusions
- 3 at 2/5 (results ambiguous, but appears to be a trend)
- 3 at 3/5 (conclusions can probably be based on the results)
- 4 at 4/5 (results are clear and very likely true)

Summary of reported teaching methods and content themes

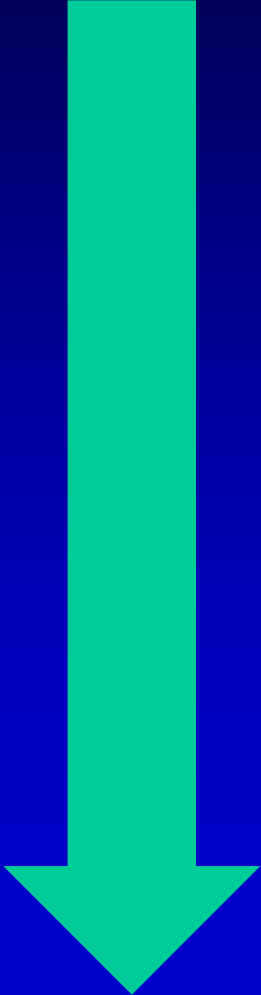| Teaching methods	Content themes:
• Group sessions/lectures • Simulation • Role-play exercises • Online materials	• Information management • Team working/leadership/communication • Error awareness and professional behaviour

Systematic Review

Steps of a Systematic Review

- Clearly formulated question

- Comprehensive data search

- Unbiased selection and extraction process

- Critical appraisal

- Analysis/synthesis of data

- **Interpretation of results**

Interpretation of Results

Some points to remember …

Challenges that a result, from a NRS review, can give a definitive answer about an intervention arise at all stages of the review

- **deciding which study designs to include**
- **searching for studies**
- **assessing studies for potential bias**
- **deciding whether to pool results**

Adequate assessment of ROB: **Biases that affect RCT also affect NRS but typically to a greater extent; regarding confounding, remember:**

- **Direction of bias is unpredictable**
- **Methods to control confounding likely varies between studies**
- **Residual confounding unknown and likely varies between studies**
- **Identify likely confounding factors which were adjusted and unadjusted**

Interpretation of Results

Some more points to remember ...

A clue to the presence of bias is notable between-study heterogeneity (but homogeneity does not indicate lack of bias)

Evaluating strength of evidence: General concern about biases in NRS, and the difficulties of attributing causality to the observed effects

- Strength of evidence provided by a SR of NRS likely depends on meeting the challenges set out
- GRADE scheme for assessing quality of a body of evidence is recommended for use in 'Summary of Findings' tables

Conducting a SR of NRS is more difficult and resource intensive than a SR of RCT, and conclusions are likely weaker and may make a relatively small contribution

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Conclusions

- Paucity of research investigating educational interventions to improve handover amongst medical and nursing staff, but growing rapidly

- Studies suggest that educational interventions can improve handover, but small sample sizes, no long-term retention data and possible publication bias limit conclusion

- Methodological quality of reported studies is generally poor

- Limited evidence demonstrating the transfer of skills to the workplace and no evidence that these interventions improve patient outcomes

Non-Randomized Studies Meeting
Ottawa, Canada

Non-Randomized Studies Meeting Ottawa, Canada

Study design and bias in nonrandomized studies

Issues relating to study design and risk of bias when including non-randomized studies in systematic reviews on the effects of interventions

Julian Higgins, PhD[1]
Craig Ramsay, PhD[2]

Some types of NRS design used for evaluating the effects of interventions

Non-randomized study (NRS)

- **Non-randomized controlled trial**
- **Controlled before-and-after study**
- **Interrupted-time-series study**
- **Historically controlled study**
- **Uncontrolled longitudinal study**
- **Cohort study**
- **Case-control study**
- **Cross-sectional study**

Some types of NRS design used for evaluating the effects of interventions

- **Non-randomized controlled trial** — People are allocated to different interventions ~~using~~ methods that are not random

- **Controlled before-and-after study** — Observations are made before and ~~after~~ implementation of an intervention, both in a group that receives the intervention and in a control group that does not

- **Interrupted-time-series study** — Observations at multiple ~~time~~ points before and after an intervention

- **Historically controlled study** — Compares a group of participants receiving an intervention with a similar group from the past who did not

- **Uncontrolled longitudinal study** — Observations are made on a series of individuals, usually all receiving the same intervention, before and after an intervention but with no control group

- **Cohort study** — Defined group of people (the cohort) is followed over time, to examine associations between different interventions received and subsequent outcomes

- **Case-control study** — Compares people with a specific outcome of interest ('cases') with people without that outcome ('controls'), to examine association between the outcome and prior exposure to an intervention

- **Cross-sectional study** — Collects information on interventions (past or present) and current outcomes for a group of people at a particular time point, to examine associations between outcomes and exposure to interventions

Study Design Features

Study Design Labels

Study Design Features

Was there a comparison:
- **Between two or more groups of participants receiving different interventions?**
- **Within the same group of participants over time?**

Were participants allocated to groups by:
- **Concealed randomization?**
- **Quasi-randomization?**
- **By other action of researchers?**
- **Time differences?**
- **Location differences?**
- **Treatment decisions?**
- **Participants' preferences?**
- **On the basis of outcome?**
- **Some other process? (specify)**

Which parts of the study were prospective:
- **Identification of participants?**
- **Assessment of baseline and allocation to intervention?**
- **Assessment of outcomes?**
- **Generation of hypotheses?**

On what variables was comparability between groups assessed:
- **Potential confounders?**
- **Baseline assessment of outcome variables?**

Non-Randomized Studies Meeting
Ottawa, Canada

Confounding and meta-analysis in nonrandomized studies

Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions

Jeffrey C. Valentine, PhD[1]
Simon G. Thompson, DSc[2]

Non-Randomized Studies Meeting
Ottawa, Canada

Selective reporting in nonrandomized studies

Issues relating to selective reporting when including non-randomized studies in systematic reviews on the effects of interventions

Susan L Norris, MD, MPH[1]
David Moher, PhD[2]

Non-Randomized Studies Meeting
Ottawa, Canada

Set of checklist for NRS have been developed based on guidance documents from workshop

How to Incorporate Non-Randomized Studies in Cochrane Reviews of Patient Safety