Managing the Study (Part 2)

John Collins
Ed Hughes

Mahone Bay

Mader's Cove


Maders Cove Rd
Loye Island
Whynot Rd
Langille Rd
Maders Cove Rd
Cove Rd
Smelt Cove
Hermans Island Rd
Creighton Dr
3
Smeltzer Rd
Buttercup Lane Cottages
Lunenburg Yacht Club
Hermans Island Rd
Hermans Point Rd
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MAHONE BAY
Population: 981

Day 1. Planning your research

Before you begin.

What is the question?

Researching the background.

The design architecture.

What to study: patients, records or publications

Internal vs external validity

Primary, secondary outcomes

Sample size assumptions.

Managing the study

CC and cohorts: consecutive accrual

Randomization: allocation sequence

Follow-up, contamination, co-intervention

Systematic review: acquisition & selection

Finishing the study Analysis plan

Relevance, funding, logistics

What is being published?

Articles 2000-2010	Number	% of Total
All AHR citations*	19,563	0.3
		% of AHR
Human	14,170	72
Epidemiological studies	3,340	17
Reviews	2,450	13
RCTs	923	5
Meta-analyses	194	1
All citations 2000-2010	6,587,780	

*Reproductive Techniques, Assisted

How many meta-analyses are published?

Articles 2000-2010	Number	% of Total
All citations*	557	
Human	506	91
Reviews (vs editorials, letters)	465	83
Meta-analyses	31	6

*Human Reproduction Update

Getting help on methods

Cochrane Handbook	Comprehensive detailed methodology for reviews ww.cochrane-handbook.org
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (replaces QUOROM) ww.prisma-statement.org
MOOSE	Meta-analysis Of Observational Studies in Epidemiology. JAMA 2000; 283:2008-12
Schlesselman, J.	A practitioner's guide to meta-analysis. Hum Reprod 1997;12:1851-63

Systematic review: definitions

Official version

Systematic reviews use pre-planned methods and an assembly of original studies that meet their criteria as 'subjects'. They synthesize the results of these primary investigations using strategies that limit bias and random error.

http://www.cochranemsk.org/cochrane/review/default.asp?s=1

Systematic review: definitions

Populist version

A **systematic review** is a literature review focused on a single question that tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question.

http://en.wikipedia.org/wiki/Systematic_review

A **Meta-analysis** is simply one of several analysis strategies that can be used to synthesize the results of a systematic review.

Steps in systematic review

1. Formulate the problem
2. Locate and select studies
3. Critically appraise the studies
4. Collect the relevant data
5. Analyze and present the results
6. Interpret the results
7. Improve and update reviews

Higgins & Green, 2009. Cochrane Handbook

Managing the study (part 2)

1. Systematic review: **acquisition** & selection

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Systematic review acquisition procedures

What literature addresses your question?

- Laboratory studies
- Epidemiological studies
- Qualitative studies
- Randomized controlled trials

Databases to search: clinical

Cochrane Central Register of Controlled Trials (CENTRAL)

MEDLINE

EMBASE

CINAHL: *Cumulative Index to Nursing and Allied Health Literature*

Acquisition procedures

The databases generally considered to be the most important sources to search are CENTRAL, MEDLINE and EMBASE.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

Other search strategies

- National and regional databases
- Subject-specific databases
- Citation indexes
- Dissertations and theses databases
- Grey literature databases
- Journals and other non-bibliographic-database sources
- Handsearching
- Conference abstracts or proceedings
- Other reviews, guidelines and reference lists Web searching

Unpublished studies (1)

A debatable subject.

- Efforts should be made to identify unpublished studies.
- Ongoing trials should be identified and tracked for possible inclusion in reviews on completion.

From Higgins and Green, 2009: the Cochrane Handbook

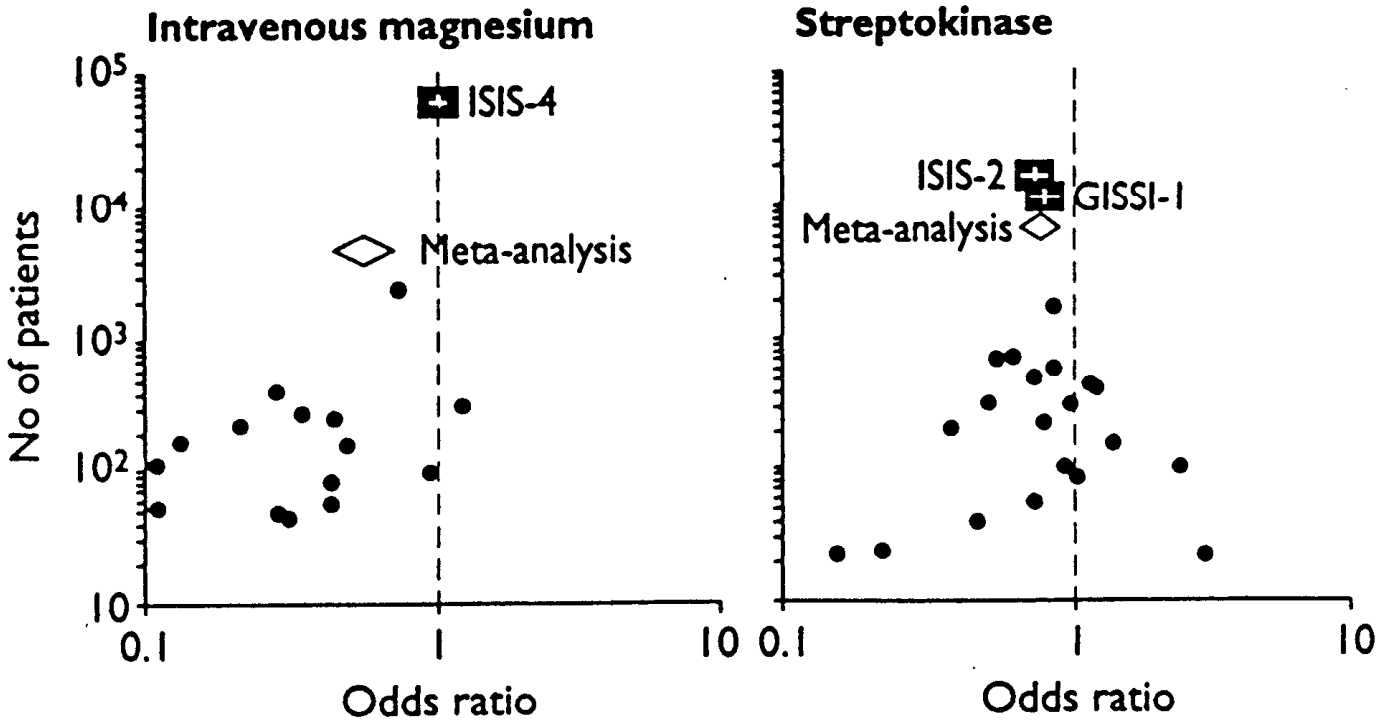
Unpublished and ongoing studies (2)

Another viewpoint.

- Studies that are published in the medical literature are available for public scrutiny. They form the basis of informed debate, and decision making by physicians, patients, regulatory agencies, and others.
- The fact that publication bias can occur serves to emphasize that much of scientific knowledge is provisional.

Schlesselman 1997. Hum Reprod 12:1851-1863. doi: 10.1093/humrep/12.9.1851

Funnel plots for meta-analyses refuted and confirmed by subsequent mega trials: intravenous magnesium (left) and streptokinase (right) in acute myocardial infarction.



Points indicate odds ratios from small and medium sized trials, diamonds indicate combined odds ratios with 95% confidence intervals from meta-analysis of these trials, and squares indicate odds ratios with 95% confidence intervals from mega trials.
(The list of trials is available from the authors)

Qualitative literature databases

CINAHL: *Cumulative Index to Nursing and Allied Health Literature*

PsycINFO

Social Sciences Citation Index

Sociological Abstracts

SAGE: Nursing and Health Sciences, Psychology, and Sociology

Broad search strategy: the exploded MeSH term "Reproductive Techniques, Assisted" includes

- Embryo Transfer
- Fertilization in Vitro
- Sperm Injection, Intracytoplasmic
- Oocyte Retrieval
- Gamete Intrafallopian Transfer
- Zygote Intrafallopian Transfer
- Sperm Retrieval
- Oocyte Donation
- Ovulation Induction
  - Superovulation
- Insemination, Artificial
  - Heterologous, Homologous
- Posthumous Conception

The MeSH term pre-implantation diagnosis has to be added.

Summary points

1. Search CENTRAL, MEDLINE and EMBASE.
2. Some topics require searching national, regional and subject-specific databases.
3. Consider conference abstracts and other grey literature.
4. Consult reference lists: other reviews, guidelines, included and excluded studies.
5. Efforts should be made to identify unpublished studies.
6. Identify ongoing trials for possible inclusion on completion.
7. Check trials registers and trials results registers.

Higgins & Green 2009; Cochrane Handbook.

Managing the study (part 2)

1. Systematic review: acquisition & **selection**

Finishing the study

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Study selection

- Set up eligibility criteria before search begins.
- Do a dry run.
- Modify the eligibility criteria if necessary.

Process for selecting studies

- **Merge search results** using reference management software, and remove duplicate records of the same report.
- **Examine titles and abstracts** to remove obviously irrelevant reports (authors should generally be over-inclusive at this stage).
- **Retrieve full text** of the potentially relevant reports.
- **Link** together multiple reports of the same study.

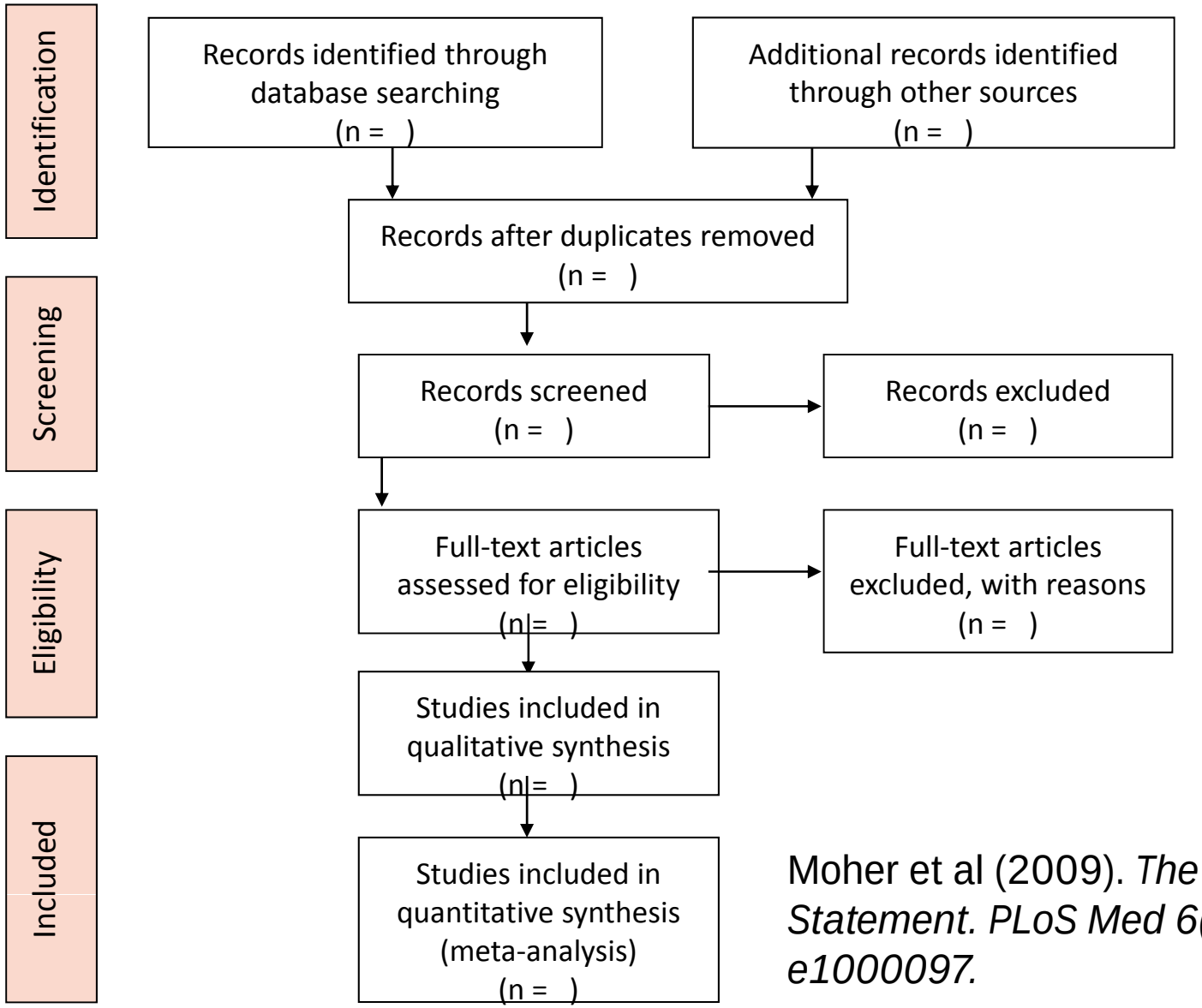
Higgins & Green 2009. Cochrane Handbook.

Process for selecting studies

- **Examine full-text reports** for compliance of studies with eligibility criteria.
- **Correspond with investigators**, where appropriate, to clarify study eligibility (it may be appropriate to request further information, such as missing results, at the same time).
- **Make final decisions** on study inclusion and proceed to data collection.

Higgins & Green 2009. Cochrane Handbook.

PRISMA 2009 Flow Diagram



Moher et al (2009). *The PRISMA Statement. PLoS Med 6(6): e1000097.*

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2. **Analysis plan**

   Depends on type of study

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Analysis plan by study type

Primary Study		Outcome	Typical Analysis
	Laboratory	Continuous	Z score, t test, regression
	Clinical	Event	chi square, logistic regression
Systematic review			
	Laboratory	Continuous	weighted mean difference
	Clinical	Event	weighted average RRs, RDs

Focus on clinical studies

Presenting risk and NNT

InVitro Fertilization with Preimplantation Genetic Screening. Mastenbroek et al, NEJM July 2007; 357 (1) 9-17

- PGS resulted in lower live birth rate*
  24% [49 of 206] vs. 35% [71 of 202]
  - absolute risk diff 11%
  - NNH 10 (1 / absolute difference)
  - Rate ratio (Relative Risk) 0.68
  - 95% CI, 0.5to 0.92
  - p=0.01

Presenting Measure of Probability: Risk vs Odds

- Risk of drawing a spade from 52 cards

= 13/52 = 1/4 =25%

- Odds of a spade from 52 cards, 1:3

= 13/39 = 1/3 = 33%

Relative Risk and Odds Ratios

	Birth	No birth	Total
PGS	a 49	b 157	206
No PGS	c 71	d 131	202
	120	288	408

RR= a/a+b / c/c+d

= 49/206 / 71/202

RR = 0.68

OR = a x d / c x b

= 49x131 / 71 x 157

OR = 0.58

Relative Risk and Odds Ratios

	Birth	No birth	Total
PGS	a 88	b 118	206
No PGS	c 128	d 74	202
	216	192	408

RR= a/a+b / c/c+d

= 88/206 / 128/202

RR = 0.68

OR = a x d / c x b

= 88x74 / 128 x 118

OR = 0.43

Presenting Measure of Probability: Risk vs Odds

- Present absolute difference (RD), relative risk (RR) and number needed to treat, to patients considering care
- Avoid odds ratios (OR) where possible

Most clinical studies use a two-by-two table

	Success	**Failure**	**Total**
Group 1	n_{11}	n_{12}	n_{1+}
Group 2	n_{21}	n_{22}	n_{2+}
Total	n_{+1}	n_{+2}	N

Diagnostic studies (disease and no disease)
Case control studies (disease and no disease)
Cohort studies
Randomized controlled trials

Analysis plan for clinical studies

1. Analyze comparability of groups
2. Chi square if no imbalance
3. Logistic regression if important imbalance
4. Report rate differences and relative risks
   (may need to convert ORs to RRs)
5. Estimate NNT where appropriate

Systematic review: assessment for bias

- **Sequence generation.**
- **Allocation concealment.**
- **Blinding of participants, personnel and outcome assessors** *Assessments should be made for each main outcome (or class of outcomes).*
- **Incomplete outcome data** *Assessments should be made for each main outcome (or class of outcomes).*
- **Selective outcome reporting.**
- **Other sources of bias.**

Higgins & Green 2009. Cochrane Handbook.

Another view of study quality

Arguments over the quality of studies, how it should be determined and what should be made of it, are in fact tangential disputes over what really is at issue, namely, which studies have the right results?

Schlesselman, J. A practitioner's guide. Hum Reprod 1997;12:1851-63

Systematic review meta-analysis

- Meta-analysis is a weighted average of individual study effects
- For example, if you bought three bags of groceries

  2 pounds of salt @ $3.00 a pound,

  3 pounds of sugar @ 1.00 a pound, and

  4 pounds of flour @ 0.45 cents a pound

  the average cost of your staple goods would be
  (2*3+3*1+4*0.45)/(2+3+4) = $1.20 per pound
- Similarly, a meta-analysis is the sum of each study's weight times its effect, divided by the sum of the all weights.

Meta-analysis methods

$$\text{generic inverse-variance weighted average} = \frac{\sum Y_i (1/SE_i^2)}{\sum (1/SE_i^2)}$$

- Y = OR, RR or RD
- $1/SE^2$ = weight = inverse of the variance.

Higgins & Green 2009. Cochrane Handbook.

Meta-analysis issues

- Heterogeneity: some factor other than the treatment is contributing to variability among the published outcomes.
- A “random effects model” considers that the individual study estimates come from a universe of possible effects, rather than from a discrete collection of studies - conservative approach
- “Fixed effects model” doesn’t address potential heterogeneity and generates more liberal (narrow) confidence intervals
- Views differ – heterogeneity invalidates a summary effect ; heterogeneity is normal: search for factors

Looking for Heterogeneity

- Clinical :
  - population
  - intervention
  - outcome
- Study quality
- Statistical :
  - I^2
  - Breslow-Day, Chi square

Extended meta-analysis

Sensitivity or sub group analysis: challenges alpha assumptions

Categorical meta-analysis

- allows exploration of factors causing heterogeneity
- allows for an adjusted mean difference between sub-groups

Meta-regression

- corresponds to linear regression
- allows for a regression co-efficient to estimate the effect of study quality, mean age, etc. on the summary relative risk.

Meta-analysis programs

Review Manager (Revman 5)	Cochrane Collaboration	ms.cochrane.org/revman
Comprehensive meta-analysis (CMA)	Biostat: NIH support	www.meta-analysis.com/
Meta-Win	No longer available	www.sinauer.com

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Logistics

Summarize from your procedures section:

- How many centres will be involved
  - What are recruitment targets
  - Multi-center management has significant issues
- Who will recruit patients?
  - Dedicated research “assistant”?
  - Process to ensure recruitment and consent done?
- How long will the study last?
  - Process to monitor recruitment targets met

Relevance

Make a statement about relevance to:

- Patients
  - How will it help them?
- body of research
  - Has question been answered at all or in less vaild way?
- clinical progress
  - Same as relevance to patients?
- funding agency
  - Be sure agency includes question in their remit

Funding

- Breakdown costs by personnel, supplies, capital costs
  - Get help with this. Important to avoid mistakes
- Consider relevant funding agencies
  - Send out for pre-review and ask others for alternative sources
- Make sure relevance section applies to the agency in question

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Summary point: start with a one-page outline.

1. **Background**
2. **Question**
3. **Planned design**
4. **Assembly**
5. **Intervention**
6. **Outcomes of interest**
7. **Analysis plan**
8. **Expected methods issues**