

Planning the Analyses

Roberta W. Scherer

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Objectives

- To explore some issues related to designing the review
- To describe issues related to the review analyses

QUORUM Statement

- The **QUORUM Statement** is a set of guidelines designed to improve the “**Quality of Reports of Meta-analyses** of randomized controlled trials”
- Published in 1999 (Moher D et al, Lancet 1999; 354:1896-1900)
- Useful to keep in mind when planning a systematic review

QUORUM Statement

- **Abstract**

objectives, data sources, review methods, results
conclusions

- **Methods**

searching, selection, validity assessment, data abstraction
study characteristics, quantitative data synthesis

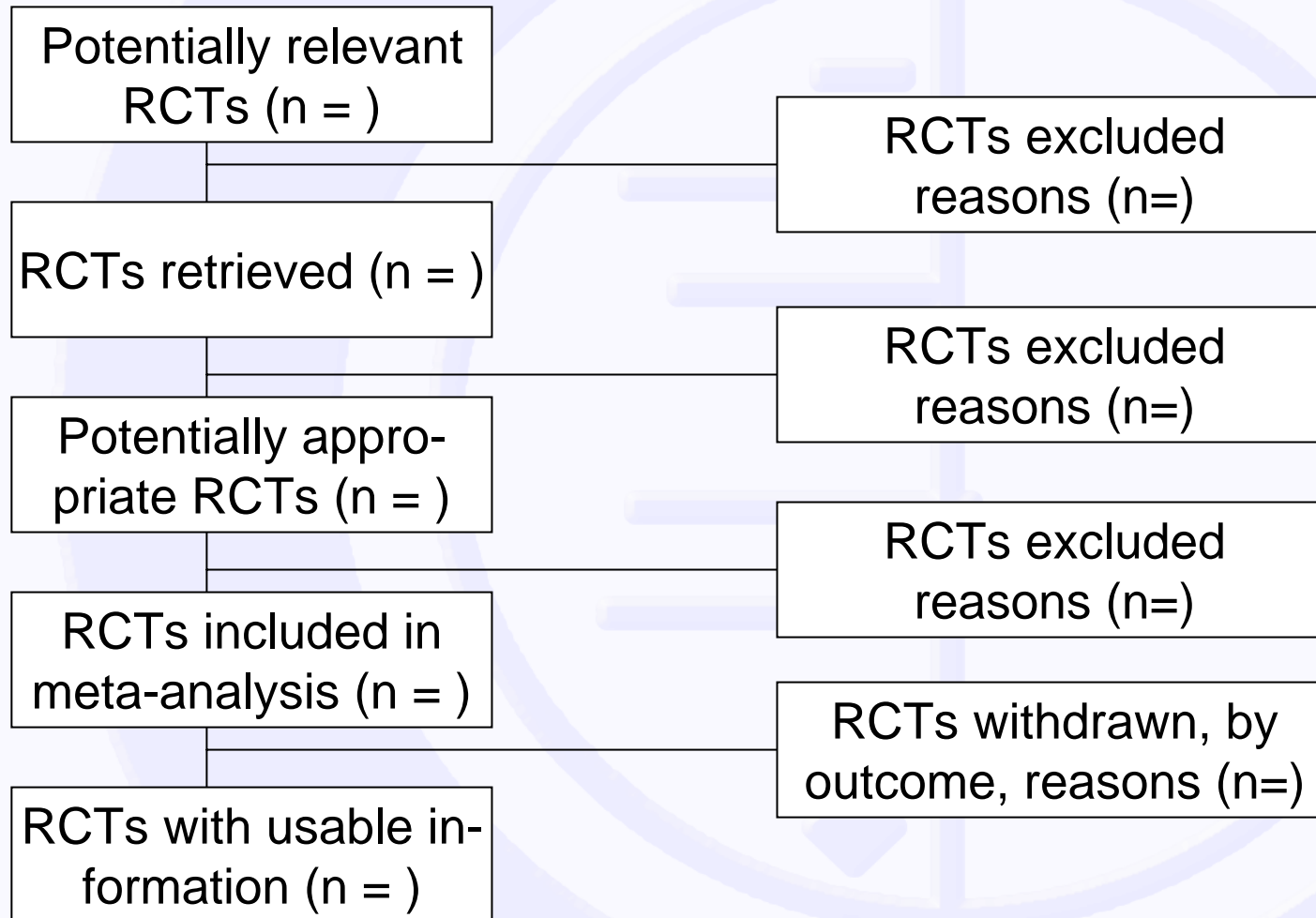
- **Results**

trial flow, study characteristics, quantitative data synthesis

- **Discussion**

summary key findings, clinical inferences, interpretation
potential biases, future research

QUORUM Flow Diagram



Analysis Section of Protocol

- Does analysis address the review **objectives**?
- How should different **trial designs** be approached?
- What form is the **outcome data** likely to be?
- What kinds of **treatment effect measures** should be used?
- Should a **meta-analysis** be done?
- How will **statistical heterogeneity** be identified and handled?

Analysis Section of Protocol 2

- What type of **meta-analysis model** should be used?
- How will **study quality** be addressed in the analysis?
- What study **characteristics** will be examined as potential causes of heterogeneity?
- How will **missing data** be handled?
- How will **publication and/or reporting biases** be handled?

Analysis Section of Protocol 3

ASK FOR HELP if needed!

Getting Started on Analyses

When thinking about the analyses, ask yourself:

- What is the **direction** of effect?
- What is the **size** of effect?
- Is the effect **consistent** across studies?
- What is the **strength of evidence** for the effect?

Types of Reviews

- **Meta-analysis** is a statistical method used to answer the first 3 questions.
 - Direction
 - Size
 - consistency
- A **Narrative Synthesis** uses subjective methods to answer these and:
 - Strength of evidence

Why Do a Meta-analysis?

- To increase power
- To improve precision
- To answer questions not posed by the individual studies
- To settle controversies arising from apparently conflicting studies
- To generate new hypotheses

When Not to Use Meta-analysis

It is best **not** to perform a meta-analysis if:

- Combining “apples with oranges”
 - Studies are clinically diverse
 - Outcomes are too diverse
- Garbage in – garbage out
 - Studies are of poor quality
 - Serious publication and/or reporting biases are present

Thinking About a Meta-analysis

The reviewer needs to consider:

- Which comparisons?
- Which study results?
- What is the best summary of effect for each comparison?
- Are study results similar for each comparison?
- How reliable are summaries?

Objectives of a Meta-analysis

- Assessment of **strength of evidence**
 - to determine whether an effect exists in a particular direction
- Statistical **pooling of results**
 - to obtain a single summary result
- Investigation of **heterogeneity**
 - to examine reasons for different results

Stages in Performing a Meta-Analysis

- Calculate a summary statistic for each study
- Calculate a summary (pooled) treatment effect estimate as a weighted average of the treatment effects estimated in the individual studies

Types of Data

- Dichotomous (or binary) data;
- Continuous data;
- Ordinal data (including measurement scales);
- Counts and rates;
- Time-to-event (typically survival)

Effect Measures for Dichotomous Data

- **Risk ratio (RR) (also called the relative risk)**
- **Risk difference (RD)**
- Odds ratio (OR)
- Number needed to treat (NNT)

Risk Ratio

Risk = number of events/number of participants

	Event		Total
	Yes	No	
Treatment	10	15	25
Control	7	18	25

Risk in Treatment Group = $10/25$ (0.40)

Risk in Control Group = $7/25$ (.28)

Risk Ratio = $0.40/0.28$ (1.43)

Risk Difference = $0.40-0.28$ (0.12)

Effect Measures for Dichotomous Data

- Risk ratio (RR) (also called the relative risk)
- Risk difference (RD)
- **Odds ratio (OR)**
- Number needed to treat (NNT)

Odds Ratio

Odds = number of events/number of non-events

	Event		
	Yes	No	Total
Treatment	10	15	25
Control	7	18	25

Odds in Treatment Group = $10/15$ (0.67)

Odds in Control Group = $7/18$ (0.39)

Odds Ratio = $0.67/0.39$ (1.72)

Effect Measures for Continuous Data

■ **Mean Difference**

- absolute difference between means of two treatment groups
- used when all trial outcome measurements use the same scale.
- called weighted mean difference (WMD) in RevMan

■ **Standardized Mean Difference**

- same outcome but measured differently
- standardized to a uniform scale

Stages in Performing a Meta-Analysis

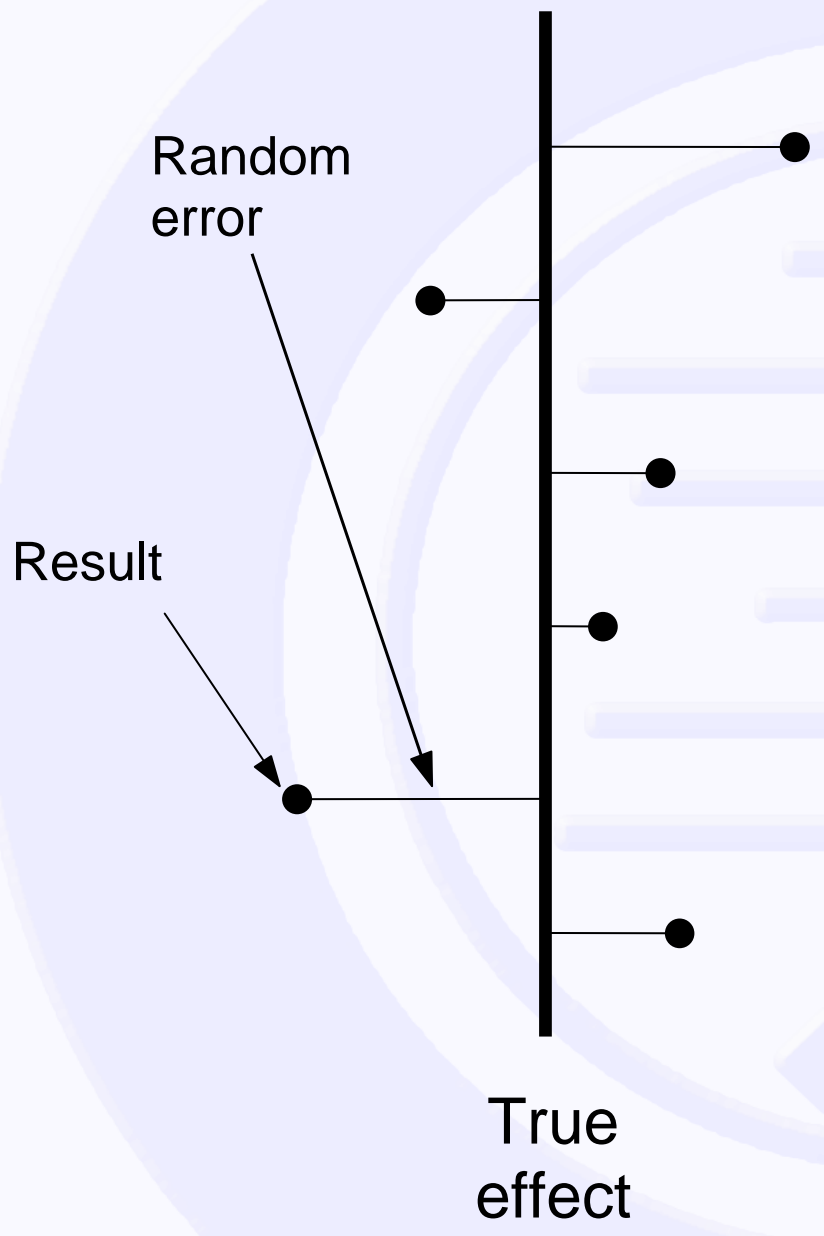
- Calculate a summary statistic for each study
- Calculate a summary (pooled) treatment effect estimate as a weighted average of the treatment effects estimated in the individual studies

Types of Meta-analytic Models

- **Fixed effects** - assumes each study is estimating exactly the same treatment effect
- **Random effects** - assumes studies are not all estimating the same treatment effect, but estimate treatment effects that follow a distribution across studies.

Fixed Effect Meta-analysis Model

(statistical homogeneity)

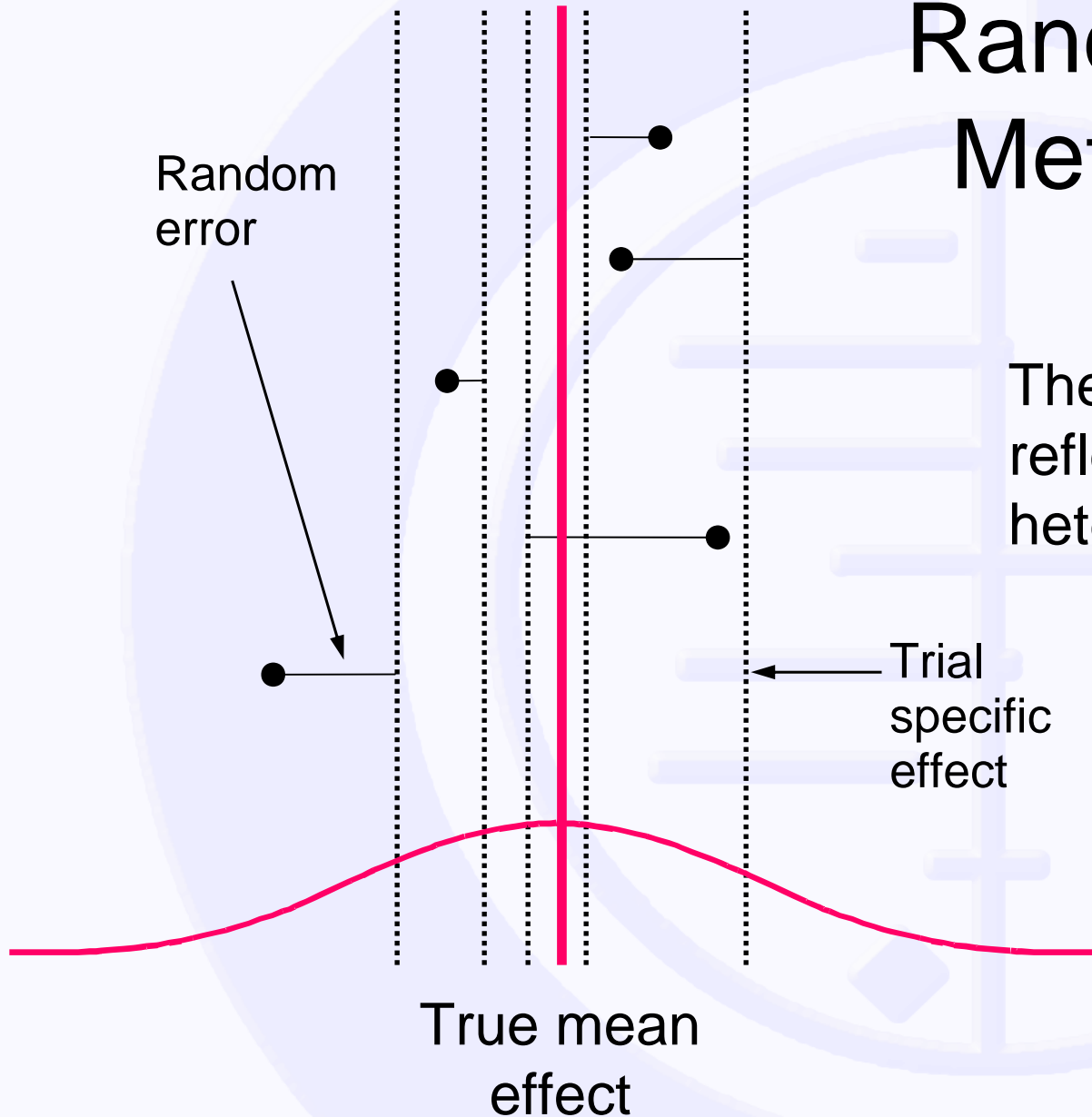


Random
error

Result

True
effect

Random Effects Meta-analysis Model



The width of the curve reflects the amount of heterogeneity

Trial specific effect

True mean effect

Diversity or Heterogeneity

- **Clinical diversity**

- Variability participants, interventions and outcomes

- **Methodological diversity**

- Variability in trial design or quality

- **Statistical heterogeneity**

- Variability in the treatment effects being evaluated
- May be due to clinical/methodological diversity among the studies
- Difference greater than expected from chance.

How to Measure Heterogeneity

- **Chi-squared test**

- Asks if differences in results are compatible with chance alone.
- BUT, has low power if trials are small or few
- A non-significant result does not mean there is no heterogeneity.

- **I-squared test**

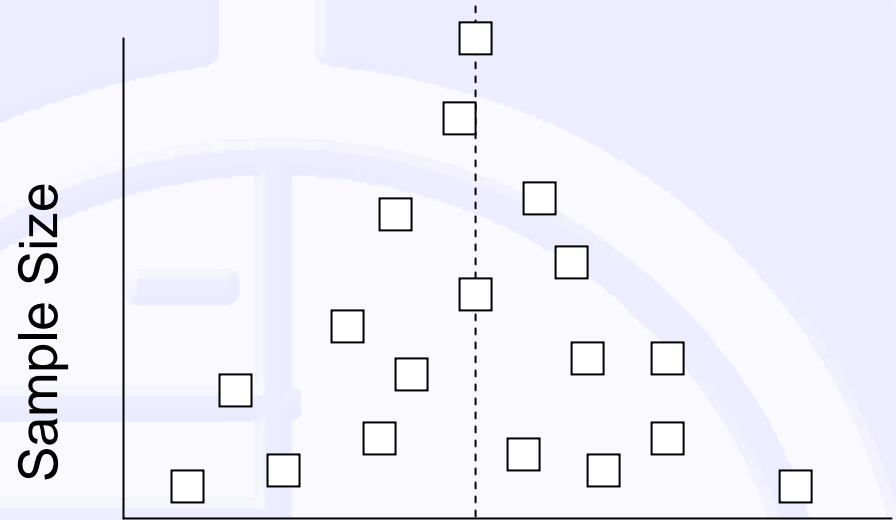
- Describes the percentage of variability due to heterogeneity rather than chance
- A value greater than 50% may be considered substantial heterogeneity

What to Do About Heterogeneity

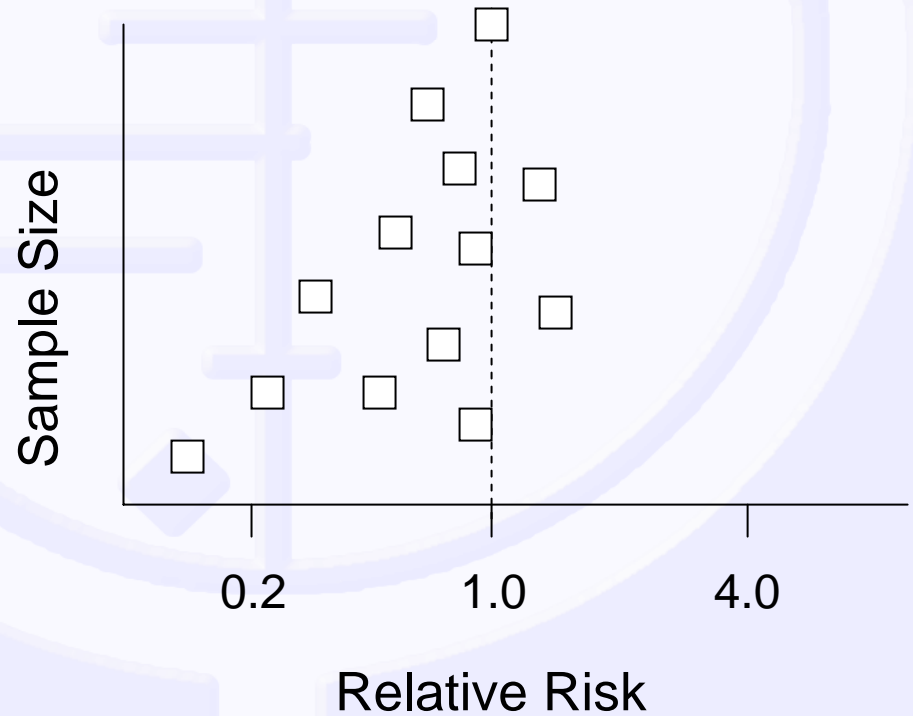
- Check that the data are correct
- Don't do a meta-analysis
- Explore the heterogeneity
- Ignore the heterogeneity
- Perform a random effects meta-analysis (instead of fixed effects)
- Change the effect measure
- Exclude studies

Funnel Plots

Symmetrical
funnel plot



Asymmetrical
funnel plot



Types of Sensitivity Analyses

- Change the inclusion criteria for studies
- Include/exclude studies if ambiguity present as to whether they meet the inclusion criteria
- Reanalyze data using a reasonable range of results for studies
- Reanalyze data imputing values for missing data
- Reanalyze data using different statistical approaches (e.g. using a random effects model instead of a fixed effect model, or *vice versa*)

Interpretation

- A common mistake when there is inconclusive evidence is to confuse 'no evidence of an effect' with 'evidence of no effect'.

Additional Resources

- Cochrane Handbook for Systematic Reviews, Chapter 8
 - <http://www.cochrane.org/resources/handbook/index.htm>
- Open Learning Materials
 - <http://www.cochrane-net.org/openlearning/HTML/mod0.htm>