King’s Trials Partnership

Minimising Bias / Measurement Error In Clinical Trials

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Overview and Objectives

• Key concepts in measurement error

• Forms of measurement error

• Accounting for measurement error

• Data management and statistical concepts

• Sources of Bias in RCTs

• Conclusion

• Matt Woolgar presents some practical examples
Key Concepts in Measurement Error

• Clinical trials are based around data collection and analysis, we wish the results to show the “true” assessment

• Error can be from systematic processes or human mistakes; in the process of recording a participants response through to the analysis

• Bias refers to a specific type of measurement error. Need to be aware of potential sources of bias in RCTs
Reliability and Validity

• Types of error that may be present in a given measure

• Refer to how a given measure relates to the truth

• Validity of accuracy of a measure (using the correct tools)
  – Sensitivity (proportion of true positives)
  – Specificity (proportion of true negatives)

• Reliability or precision of a measure
  – Over repeated measures (reducing variation)
Types of Measurement Error

• Systematic or non random error.
  – Common form of assessor error
  – Measures vary between trial arms
  – Measure vary between case severity
  – Can lead to information bias

• Random error
  – Mistakes are unpredictable
  – Occur independently of other values or variables in the study
  – Randomisation should ensure balance
  – BLINDING to study information, mistakes occurring independently of other variables
  – Ensure sample size is large enough!
Variable Form

• Impact of measurement error on a study can depend on the form of the variable involved

• Continuous and categorical variables leading…..
  – Dichotomous variables

• Differential misclassification (systematic error)

• Non-differential misclassification (random error)

• Loss of information!
Forms of Measurement Error / Impact

- Random error: Dilution of treatment effect
- Systematic error: Outcome could appear different for various groups
- Error in recording of potential confounding variables: Importance of stratification.
Accounting for the Effects of Measurement error

- Design, researchers consider the validity/reliability of the measures they employ

- Perform sensitivity analyses to assess levels of systematic bias

- Discuss errors (random or systematic) in the study conclusions
Data Management

• Different levels of access to the data storage system

• Different databases for therapist / compliance information

• Use of an AUDIT trail

• Correct interpretation of validated questionnaires of data collection tools

• Data monitoring
Statisticians

• Maintain Statistician Blind
  – Open and closed DMEC reports
  – Minute-ing of statistician blind
  – Protection from potentially unblinding data
  – Writing the analysis plan prior to exposure to the data and randomisation groups
Sources of Bias in Clinical Trials

- Reliability of the results of a RCT depends on the extent to which potential sources of bias have been avoided.

- **Selection bias**: systematic differences between baseline characteristics of the groups that are compared.
- Successful randomisation prevents selection bias in allocating interventions to participants.

- **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 study participants and personnel may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes.
- Effective blinding may ensure that the trial arms receive a similar amount of attention, ancillary treatment and diagnostic investigations.
- Blinding is not always possible, however, ensure the maximum levels of blinding possible
Sources of Bias in Clinical Trials

- **Detection bias**: systematic differences between groups in how outcomes are determined.
- Blinding of outcome assessors may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement. Very important for assessment of subjective outcomes such as pain.

- **Attrition bias**: systematic differences between groups in withdrawals from a study. Withdrawals from the study lead to incomplete outcome data.

- **Reporting bias**: systematic differences between reported and unreported findings. Within a published report those analyses with statistically significant differences between intervention groups are more likely to be reported than non-significant differences.

- **Other biases**: Other sources of bias
  - Relating to specific trial designs, for example in a cross-over trial-contamination whereby the experimental and control interventions get ‘mixed’
Concluding Remarks

• Be more aware of potential sources of error at the design stage

• Ensure robust randomisation and blinding processes

• Reflect critically on the potential impact of error /bias in your study
References

