



**Mahidol University**

Faculty of Medicine Ramathibodi Hospital

Department of Clinical Epidemiology and Biostatistics

# **Journal Club**

## **“Choice of Mean Difference Estimation for Meta-analysis of Continuous Outcomes:**

## **Final values, Change scores, and ANCOVA”**

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# Topic Overview

- Introduction
- Meta-analysis of change score: Recommendation from Cochrane Handbook for Systematic Reviews of Interventions



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# Introduction

# Meta-analysis of Continuous Outcomes

- **The term 'continuous'** in statistics conventionally refers to a variable that can take any value in a specified range.
- When dealing with numerical data, number may be measured and reported to **an arbitrary number of decimal places**.
  - Example: weight, area, and volume
- Meta-analyses of continuous outcomes are recognized to be **more challenging** than those with binary outcomes.

# Effect Size Measurement

- In meta-analyses of continuous outcomes, **the common effect size measurements** are as follow:
  - Mean difference (MD)
  - Standardized mean difference (SDM)
  - Ratio of means (RoM)
- The choice of the two most commonly used effect size measures (MD and SDM) is mainly **determined by the scale of measurement.**
- If the scale of measurement is similar as in HbA1c, the MD can be used to aggregate effect sizes across studies.

# Pooling Effect size

- To pool the effect sizes of continuous outcomes, it is important to consider whether **the baseline MD of the outcome data** between the intervention and control groups **is adequately balanced**.
- **Baseline imbalance can result from:**
  - Chance especially in small trials
  - Selection bias due to inadequate allocation concealment
  - Poor randomization
- Therefore, in meta-analysis, it is important to consider accounting **for baseline imbalance** and **pre/post correlation**.
- However, the meta-analyses available have not taken into account a specific methodological challenge posed by baseline imbalances between groups.

# Choice of Mean Difference Estimation

- **Choice of mean difference estimation:**
  - Simple analysis of change scores (CS)
  - Simple analysis of final values (FV)
  - Analyses of Covariance (ANCOVA)
- Meta-analyses of RCTs reporting continuous outcomes with **high baseline imbalances** require adjustments using an **ANCOVA procedure** effect size estimator at a pooled and individual study levels.
- ANCOVA produces a relatively **more precise effect size estimate** than CS and FV.

# Choice of Mean Difference Estimation

- There is methodological guidance available to employ ANCOVA effect size.
- **Limitation of ANCOVA for meta-analysis:**
  - The unavailability of summary data from RCTs
  - Absence of individual participant data (IPD)
  - The complexity of the ANCOVA methodology

# Choice of Mean Difference Estimation

- Three commonly used estimators are the final value (FV), change score (CS), and analysis of covariance (ANCOVA) estimator

$$\hat{\theta}_{FV} = \bar{y}_{int} - \bar{y}_{ctrl}$$

$$\hat{\theta}_{CS} = (\bar{y}_{int} - \bar{y}_{ctrl}) - (\bar{x}_{int} - \bar{x}_{ctrl})$$

$$\hat{\theta}_{ANCOVA} = (\bar{y}_{int} - \bar{y}_{ctrl}) - \beta(\bar{x}_{int} - \bar{x}_{ctrl})$$

where  $\beta = \rho \frac{\sigma_y}{\sigma_x}$

# Some observations from comparing the analytical methods

## Estimates of intervention effect:

- For a particular data set, the three estimators can produce different estimates of intervention effect.
  - When the correlation (btw baseline value and final value) is close to 0,  $\hat{\theta}_{\text{ANCOVA}} \approx \hat{\theta}_{\text{FV}}$
  - When the correlation (btw baseline value and final value) is close to 1,  $\hat{\theta}_{\text{ANCOVA}} \approx \hat{\theta}_{\text{CS}}$
- **Over the data sets (varying correlation), the ANCOVA estimate varies**, however, a simple analysis of either change scores (CS) or final values (FV) dose not.

# Some observations from comparing the analytical methods

## Standard errors:

- The standard error (SE) of the FV estimator remains the same over all data sets.
- As the correlation increases, the SE of the CS estimator decreases.
  - When the correlation  $< 0.5$ , the SE of CS estimator is  $>$  SE of FV estimator.
  - When the correlation  $> 0.5$ , the SE of CS estimator is  $<$  SE of FV estimator.
- For a particular data set, the SE of the ANCOVA estimator is smaller compared to the SEs of FV and CS.

# Relationship Between the Estimators

$$\hat{\theta}_{ANCOVA} = (\bar{y}_{int} - \bar{y}_{ctrl}) - \beta(\bar{x}_{int} - \bar{x}_{ctrl})$$

- **Assuming  $\sigma_y^2 = \sigma_x^2$ :**
  - When the correlation is close to 0,  $\beta \approx 0$ ;  $\hat{\theta}_{ANCOVA} \approx \hat{\theta}_{FV}$
  - When the correlation is close to 1,  $\beta \approx 1$ ;  $\hat{\theta}_{ANCOVA} \approx \hat{\theta}_{CS}$
- When there is minimal baseline imbalance, the three methods produce similar estimates since

# Statistical properties of the estimators: Unconditional inference

- How do the estimators perform over hypothetical repetitions of RCTs where baseline imbalance randomly varies?
- **Bias:**
  - FV, CS, and ANCOVA are unbiased.
  - Type I error rates will be designated.
- **Precision:**
  - ANCOVA is (generally) more efficient compared with FV, or a CS.

# Statistical properties of the estimators: Conditional inference

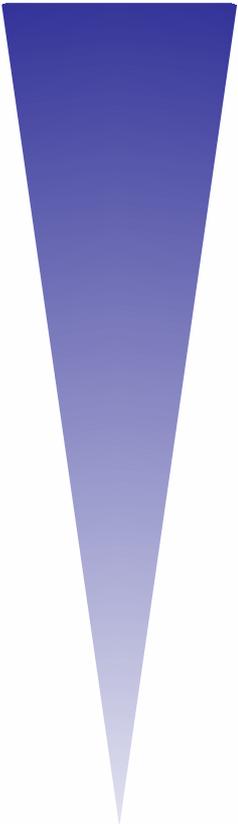
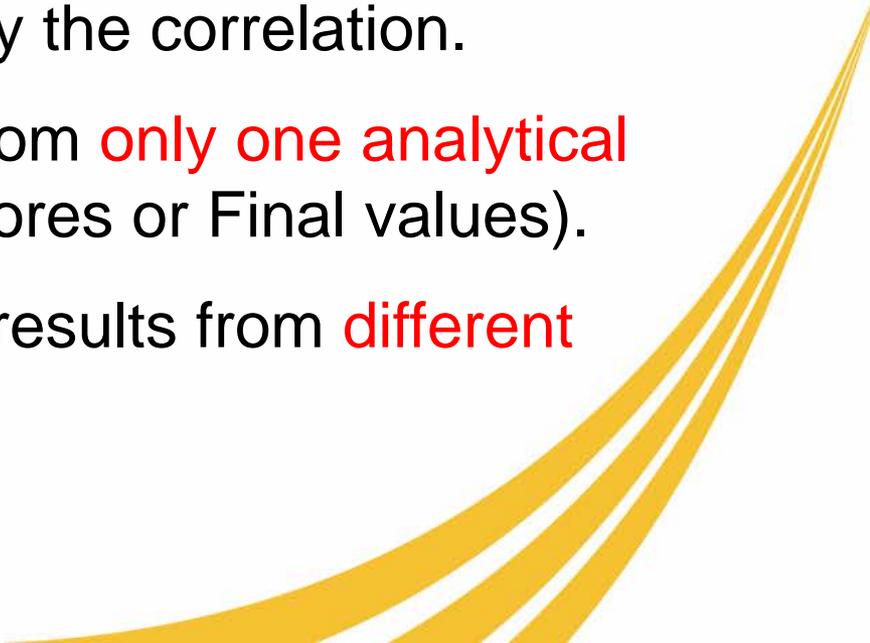
- How do the estimators perform over hypothetical repetitions of RCTs with the same baseline imbalance?
- **Bias:**
  - ANCOVA is conditionally unbiased.
  - FV and CS is conditionally biased.
- **Precision:**
  - ANCOVA is (generally) more efficient compared with FV, or a CS.
- **ANCOVA is the preferred** analytical method both conditionally and unconditionally.

# Meta-analysis in the real world

- **In publication of trials:**

- Generally **only one type of analysis** will be reported.
  - **Less frequently**, an alternative analysis will be provided, or enough information to allow an alternative analysis to be performed.
- The analytical method used may (is likely to) vary across trials.

# Meta-analysis Options: A proposed hierarchy of options

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1. Obtain **individual patient data** for each trial and re-analyze these data.
  2. **Pool using only ANCOVA results.** For each trial, recreate the ANCOVA estimate from the summary statistics provided. This will generally involve imputing only the correlation.
  3. Pool using results from **only one analytical method** (Change scores or Final values).
  4. Pool using a mix of results from **different analytical methods.**
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# **Meta-analysis of Change Score: Recommendation from Cochrane Handbook for Systematic Reviews of Interventions**

# Meta-analysis of Change Score

- An analysis based on **changes from baseline (CS) will be more efficient and powerful** than comparison of final values (FV).
  - **Remove between-person variability** from the analysis
- However, calculation of a change score (CS) requires **measurement of the outcome twice**.
- In practice **may be less efficient** for outcomes which are unstable or difficult to measure precisely.
- Change-from-baseline outcomes (CS) may also be preferred if they have **a less skewed distribution** than final measurement outcomes (FV).
- Although sometimes used as a device to ‘correct’ for unlucky randomization, this practice is not recommended.

# The Preferred Statistical Approach

- **The preferred statistical approach** to accounting for baseline measurements of the outcome variable:
  - **A regression model** by include the baseline outcome measurement as a covariate in the model
  - **ANCOVA**
- These analyses produce **an 'adjusted' estimate of the treatment effect** together with its standard error.
  - The most precise
  - The least bias
- They should be included in the analysis when they are available.
- They can only be included in a meta-analysis **using the generic inverse-variance method**, since means and SD are not available for each intervention group separately.

# Change Score vs Final value

- **In practice**, an author is likely to discover that the studies included in a review may include **a mixture of CS and FV**.
- However, mixing of outcomes **is not a problem** when it comes to meta-analysis of mean differences.
- There is no statistical reason why studies with CS should not be combined in a meta-analysis with studies with FV when using the (unstandardized) mean difference method.

# Change Score vs Final value

- **In a RCT**, mean differences based on CS can usually be assumed to be addressing **exactly the same underlying intervention effects** as analyses based on FV.
- The difference in FV will **on average be the same as** the difference in CS.
- If the use of CS does increase precision, **the studies presenting CS** will appropriately be **given higher weights** in the analysis than they would have received if FV had been used, as they will **have smaller SD**.

# Pooling Change Score and Final Value

- When combining the data, authors must be careful to **use the appropriate means and SD** (either of CS or FV) for each study.
- **Since the mean and SD for the two types of outcome may differ substantially**, it may be advisable to **place them in separate subgroups** to avoid confusion for the reader, but the results of the subgroups **can legitimately be pooled together**.

# Pooling Change Score and Final Value

- However, **CS and FV should not be combined together as SMD**, since the difference in SD reflects not differences in measurement scale, **but differences in the reliability of the measurements**.
- **A common practical problem** associated with including CS is that **SD of changes is not reported**. Imputations of SD is needed.



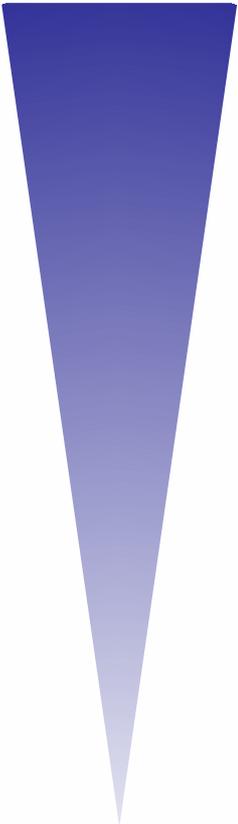
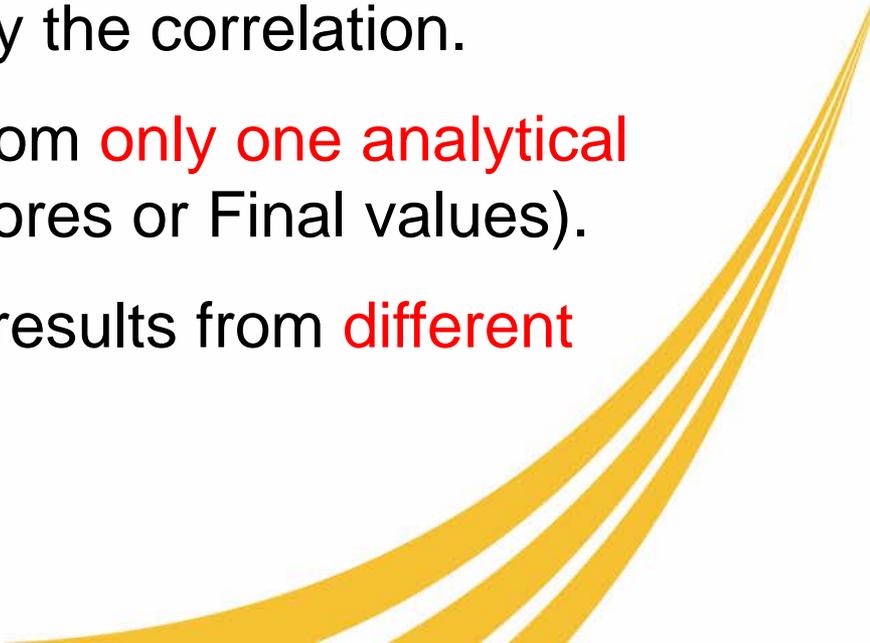
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# Summary

# Meta-analysis Options: A proposed hierarchy of options

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# References

- Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0
- Cochrane Statistical Methods Group: Short Courses  
SMG Training Course 2010 Slides  
(<https://methods.cochrane.org/statistics/>)



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**... Thank you ...**