Meta-analytic Methods and Cluster Randomised Trials

Ulrich Mansmann
IMBI, University of Heidelberg
Overview

Introduction

Meta-analytic approach to CRTs

Meta-analysis of cluster randomised trials

Meta-analysis considering both:
  individually and cluster randomized trials

Summary, References
RCT versus CRT

I+R I+R
P P
C P P P P
O O O O

I Intervention
R Randomisation
C Cluster
P Patient
O Observation
Introduction

Four defibrillator studies

My first encounter with CRTs was MA:

Summarise the difference in success rates for two different algorithms implemented in cardio-defibrillator from 4 randomised studies.

Patients were randomised to a defibrillator with one of the two algorithms under study.

But each patient is a cluster of observations:
During the study period there are many situations/events which have to be handled successfully by the defibrillator. Count for each patient the total number as well as the number of successful events.
Surgical example

• Does a new standardised surgical concept for patients with colorectal cancer improve 5 year survival?

• Covariates on patient level: prognostic factors
  Covariates on surgeon level: experience, attitude
  Covariates on centre level: quality of care

• One surgeon will not be able to apply old and new concept in his practice following a random assignment.
  There are two options:
  Train different surgeons in each centre
  Train all surgeons of selected centres
MA approach to CRT

ANALYSIS OF CLUSTER RANDOMIZED TRIAL USING MULTI-LEVEL MODEL

Figure 1 of Omar RZ, Thompson SG (2000) *Analysis of CRT using a multi-level model*, SIM, 19, 2675-2688
MA approach to CRT

Fixed effects

Effect measure - Odds or log(Odds) in control or intervention group

\[ \hat{\theta}_{\text{group,cluster}} = \theta_{\text{group}} \]

\[ \hat{\theta}_G \sim N(\theta_G, \sigma^2_G) \]

\[ \hat{\theta}_G = \frac{\sum w_i \hat{\theta}_i}{\sum w_i} \quad w_i = \frac{1}{s_i^2} \quad s_G^2 = \frac{1}{\sum w_i} \]

\[ \Delta_{IK} = \hat{\theta}_I - \hat{\theta}_K, \quad s_\Delta = \sqrt{s_I^2 + s_K^2} \quad [\Delta_{IK} - 1.96 \cdot s_\Delta, \Delta_{IK} - 1.96 \cdot s_\Delta] \]

\[ Q_{IK} = \frac{\hat{\theta}_I / \hat{\theta}_K}{\sum \frac{\hat{\theta}_i^2}{\hat{\theta}_K^2}} \quad s_{Q_{IK}} = \frac{1}{\hat{\theta}_K} \sqrt{s_I^2 + \frac{\hat{\theta}_I^2}{\hat{\theta}_I^2} s_K^2} \quad [Q_{IK} - 1.96 \cdot s_{Q_{IK}}, Q_{IK} + 1.96 \cdot s_{Q_{IK}}] \]
What is $\sigma^2$?

$$s_i^2 = \frac{\hat{p}_i \cdot (1-\hat{p}_i)}{n_i} \cdot \text{IF}$$

$$\text{IF} = \frac{\text{Var}_{\text{Cor}}}{\text{Var}_{\text{Ind}}}$$

$$\text{Var}_{\text{Cor}}(p) = \frac{1}{n \cdot \bar{m}^2} \cdot \frac{\sum a_i^2 - 2 \cdot p \cdot \sum a_i m_i + p^2 \sum m_i^2}{n - 1}$$
MA approach to CRT

Random effects

Effect measure - Odds or log(Odds) in control or intervention group

\[ \theta_{\text{group,cluster}} = \theta_{\text{group}} \]

\[ \tau^2 = \max\{0, \sum_{i=1}^{n} w_i \cdot (\hat{\theta}_i - \hat{\theta}_G)^2 - (n - 1) \} \]

\[ w_i = \frac{1}{s_i^2} \]

Use the same formulae as for fixed effect with weights \( w^* \).

\[ w_i^* = \frac{1}{s_i^2 + \tau^2} \]
### MA of CRTs

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<th>Trial country</th>
<th>Intervention</th>
<th># cluster</th>
<th># events</th>
<th># subjects</th>
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<td><strong>4.2</strong></td>
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Effect of a new antenatal care programme on hypertension during pregnancy
MA of CRTs

How to analyse such data?
1. Modified Mantel-Haenszel procedure
2. Woolf’s procedure
3. GEE or hierarchical model
MA of CRTs

Modified Mantel-Haenszel procedure

\[ \hat{\psi}_{\text{Cluster}} = \frac{\sum_{j=1}^{J} W_j \hat{\psi}_j}{\sum_{j=1}^{J} W_j} \]

\[ \hat{\psi}_j = \frac{\hat{P}_{\text{Int},j} \cdot (1 - \hat{P}_{\text{Con},j})}{\hat{P}_{\text{Con},j} \cdot (1 - \hat{P}_{\text{Int},j})} \]

\[ P_{\text{Int},j} = \frac{E_{\text{Int},j}}{M_{\text{Int},j}} \]

\[ W_j = \left[ \frac{C_{\text{Int},j}}{M_{\text{Int},j}} + \frac{C_{\text{Con},j}}{M_{\text{Con},j}} \right]^{-1} \cdot \left(1 - \hat{P}_{\text{Int},j}\right) \cdot P_{\text{Con},j} \]

\[ C_{\text{Int},j} = \sum_{k=1}^{n_{\text{Int},j}} m_{\text{Int},j,k} \cdot \left[ 1 + (m_{\text{Int},j,k} - 1) \cdot \hat{\rho} \right] / M_{\text{Int},j} \]

CRT \( j \),

\( M_{\text{Int},j} \) - size of intervention group in CRT \( j \)

\( m_{\text{Int},j,k} \) - size of cluster \( k \) with intervention in CRT \( j \)

\( E_{\text{Int},j} \) - # of events under intervention in CRT \( j \)

How to estimate trial specific cluster effect?

Generalized Chi² statistic to test for general effect.
MA of CRTs

Woolf’s procedure

Combining a small number of CRTs, each of fairly large size

\[
\hat{\gamma}_{\text{Cluster}} = \frac{\sum_{j=1}^{J} W_j \hat{\gamma}_j}{\sum_{j=1}^{J} W_j} \quad \text{Var}[\hat{\gamma}_{\text{Cluster}}] = S_C^2 \cdot \sum_{j=1}^{J} W_j^2 / \left( \sum_{j=1}^{J} W_j \right)^2
\]

\[
\hat{\gamma}_j = \log[\hat{\Psi}_j] = \log \left[ \frac{\hat{P}_{\text{Int},j} \cdot (1 - \hat{P}_{\text{Con},j})}{\hat{P}_{\text{Con},j} \cdot (1 - \hat{P}_{\text{Int},j})} \right] \quad \hat{P}_{\text{Int},j} = E_{\text{Int},j} / M_{\text{Int},j}
\]

\[
W_j = \left[ \frac{1}{M_{\text{Int},j}} + \frac{1}{M_{\text{Con},j}} \right]^{-1} (1 - \hat{P}_{\text{Int},j}) \cdot P_{\text{Con},j}
\]

\[
S_C^2 = \sum_{j=1}^{S} W_j (\hat{\gamma}_j - \hat{\gamma}_W)^2 / \sum_{j=1}^{S} W_j
\]
MA of CRTs

GEE, hierarchical models, individual data

Population averaged approach:

\[ P[y_{ij}=1 \mid X_{ij}] = \{1+\exp(-\alpha^* - \beta^* \cdot X_{ij})\}^{-1} \]

\( \beta^* \) is looking at changes between people

\[ | \beta^* | \leq | \beta^# | \]

Cluster specific approach:

\[ P[y_{ij}=1 \mid \alpha_i ,X_{ij}] = \{1+\exp(-\alpha_i - \beta^# \cdot X_{ij})\}^{-1} \]

\( \alpha_i \) vary with distribution \( f(\alpha) \)

\( \beta^# \) is looking at changes within people
MA of CRTs

GEE, hierarchical models, individual data

Both allow an extension of standard logistic regression which adjusts for the effect of clustering.

Model \( \log \left( \frac{P_{ijkl}}{1-P_{ijkl}} \right) \) as a linear function of covariates. 

\( P_{ijkl} \) prob. of success for individual \( l \) belonging to cluster \( k \) in group \( i \) of trial \( j \).

GEE approach: Define indicator variables for the trials included. 
Use appropriate working covariance structure (Compound symmetry) 
Estimate the OR related to intervention (CI, test).

Hierarchical: Define additional to the cluster specific hierarchy a trial specific hierarchy and estimate the OR related to the intervention (CI, test).
MA containing CRTs and RCTs

Example


4 hospital based trials with individual randomization (children with measles)
8 community and household based trials (healthy children)
average cluster size (household): 2

Make two different MAs - if results agree, this is a strong argument to support the intervention

Make one combined analysis
- if trials are similar enough
- if interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely

Set cluster effect parameter in MH-statistics or Woolf’s approach for the corresponding study to 1 ($C_{int,j} = C_{Con,j} = 1$)
Adjust structure of working correlation matrix or random effects.
Summary

• CRTs offer additional sources of study heterogeneity
  Nature of randomisation unit: household, community, worksite,...
  Sizes and number of clusters
  Methodological quality

• Published data makes it difficult to estimate design-effects
  Use of external estimates may at times be necessary

• Meta-analysis of matched pairs and stratified designs
  break up pair matching, analyse like completely randomised designs.
References


