Exploring The Effect Of Patient Characteristics On Effectiveness Using A Combination Of Individual Subject And Aggregate Level Data

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Application: Meta-analysis of home safety education and the provision of safety equipment for the prevention of childhood accidents in the home

- Strong emphasis on exploring whether effectiveness is related to socio-demographic characteristics
- Individual participant covariate data allows a much more powerful analysis compared to summary level covariates
  - Decided to (attempt to) obtain the individual participant data (IPD)
- Included cluster and non-cluster allocation studies
- Mixture of randomised & quasi randomised studies

. . . . . But IPD data only available from a proportion of studies:

- Of the 27 studies eligible for one or more meta-analysis outcome, 11 provided IPD

How proceed when exploring socio-demographic covariates?

Option 1: Exclude all studies which do not have individual participant level covariates of interest

- Disadvantage: Excludes majority of otherwise eligible studies

Option 2: Only do a summary level analysis of covariates. (e.g. a meta-regression on proportion of study subjects with characteristic of interest)

- Disadvantage: Does not utilize the advantages of the IPD data obtained

- Option 3: Develop an option 3!

Option 3: Objective

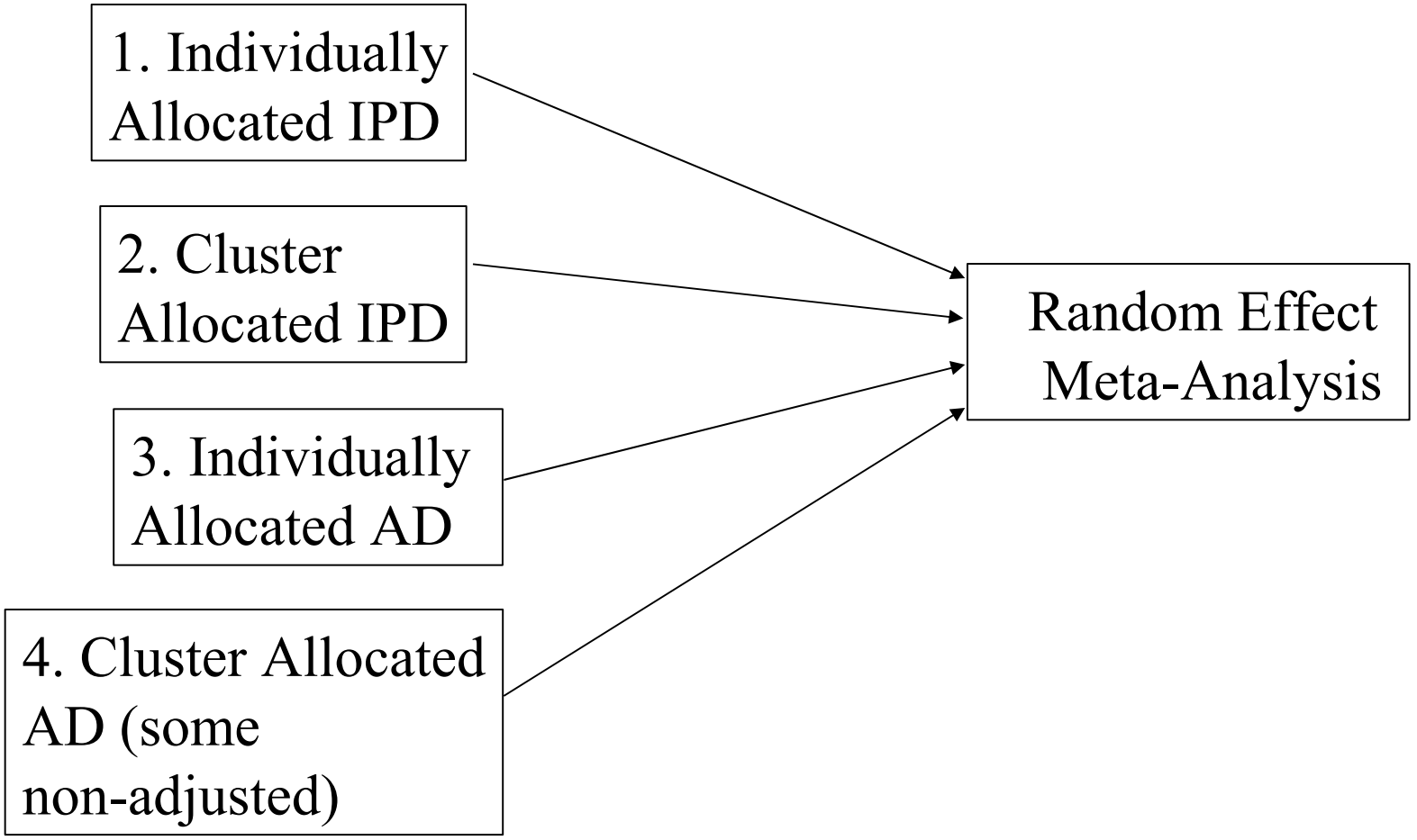
- To develop a (random effects) meta-analysis model that could meta-analyse both individual subject and aggregate level (binary) outcome data while exploring the effects of subject level (binary) covariates available in a combination of individual subject and aggregate level

- Additionally, want to deal with the clustering in the clustered designed studies appropriately

Philosophical Approach

- To estimate an intervention effect & covariate effect from each study individually you would fit a different statistical model for each of the 4 study/data combinations
- Usually we have the same data format and fit one common model in meta-analysis
- Relax this assumption and write a custom model for each study/data combination

Schematic of the study/data types to combine



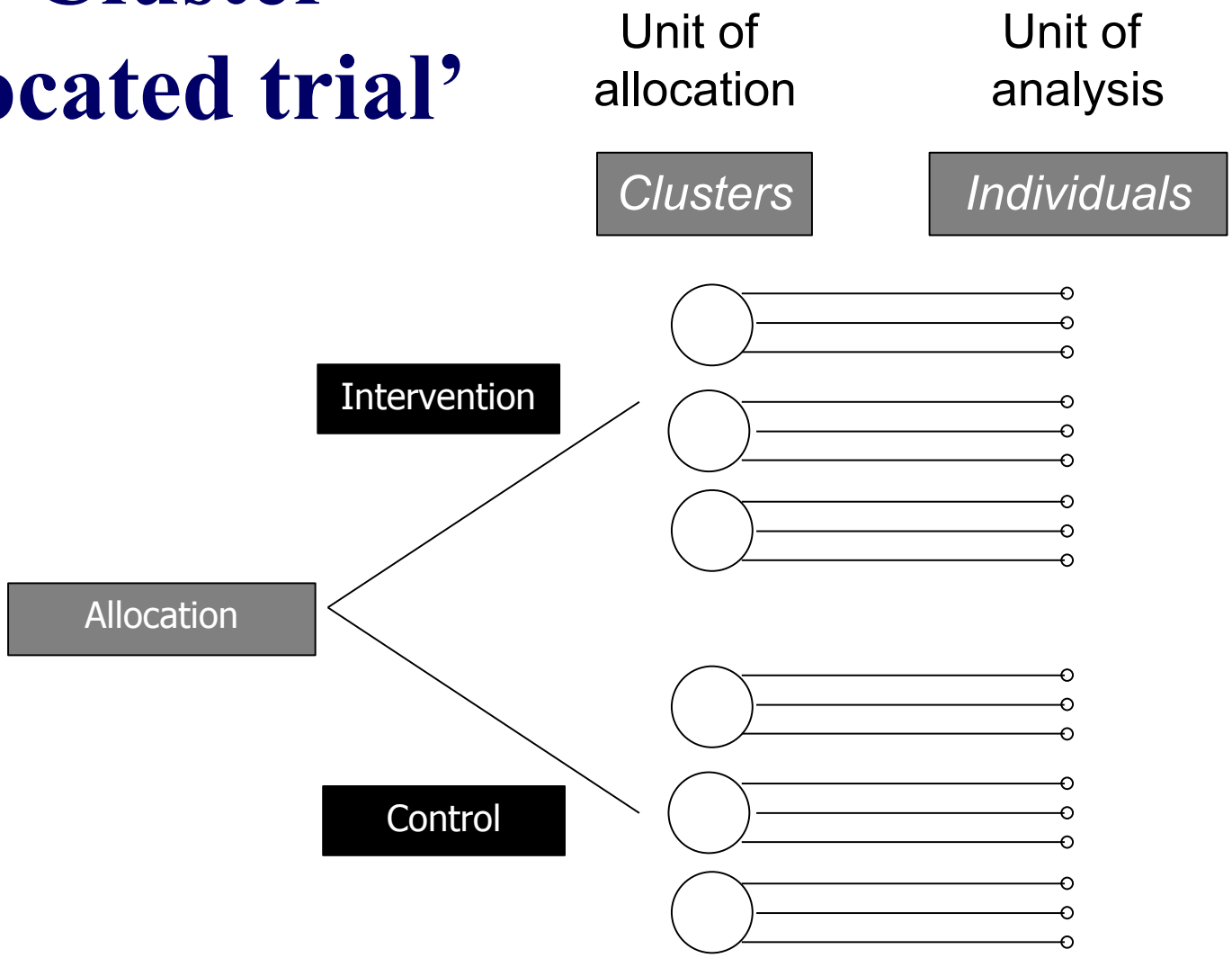
Practical Approach

- This is clearly not going to be possible using “off the shelf” meta-analysis software (RevMan or other)
- But statistical models have been described in the literature for the meta-analysis of each of the 4 study/data combinations *individually*
- Need to use all 4 models in one meta-analysis

Practical Approach II

- In my opinion, the Bayesian package WinBUGS is the most flexible for specifying "non-standard" statistical models such as this
- This aspect of Bayesian analyses is often overshadowed by issues surrounding prior distributions
- 2 main issues dealt with in turn:
  - 1) Taking into account clustering effect
  - 2) Adding study and participant level covariates

‘Cluster allocated trial’



Cluster allocated studies

- The problem is
  - Two subjects in one cluster are likely to behave more similarly than two patients from different clusters…
- Award the study higher precision (more weight) than it deserves if not taken into account

Extremes:

- Suppose everyone in a cluster were identical
  - Then effective size of trial = number of clusters
- Suppose there is no particular similarity within a cluster
  - Then effective sample size = number of individuals
- In practice, effective size of trial is somewhere between number of participants and number of clusters

Design effect

Average cluster size

Design effect = $1 + (n - 1) \times \rho$

Intra-class correlation coefficient (ICC)

$$= \frac{\sigma^2_B}{\sigma^2_W + \sigma^2_B}$$

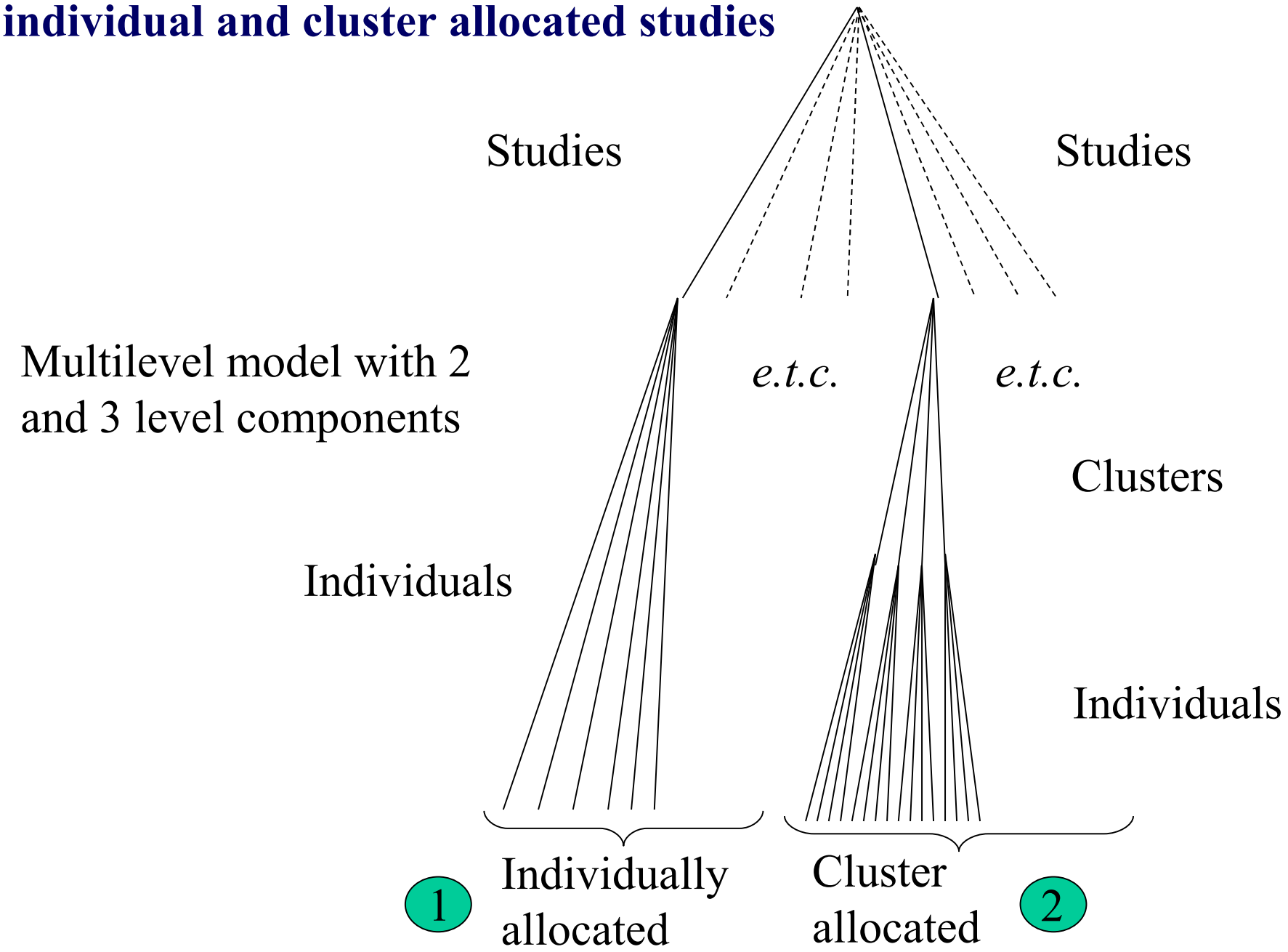
- Estimate of ICC could be obtained from a) paper (unlikely);
  b) external sources

Cluster allocated studies in meta-analysis

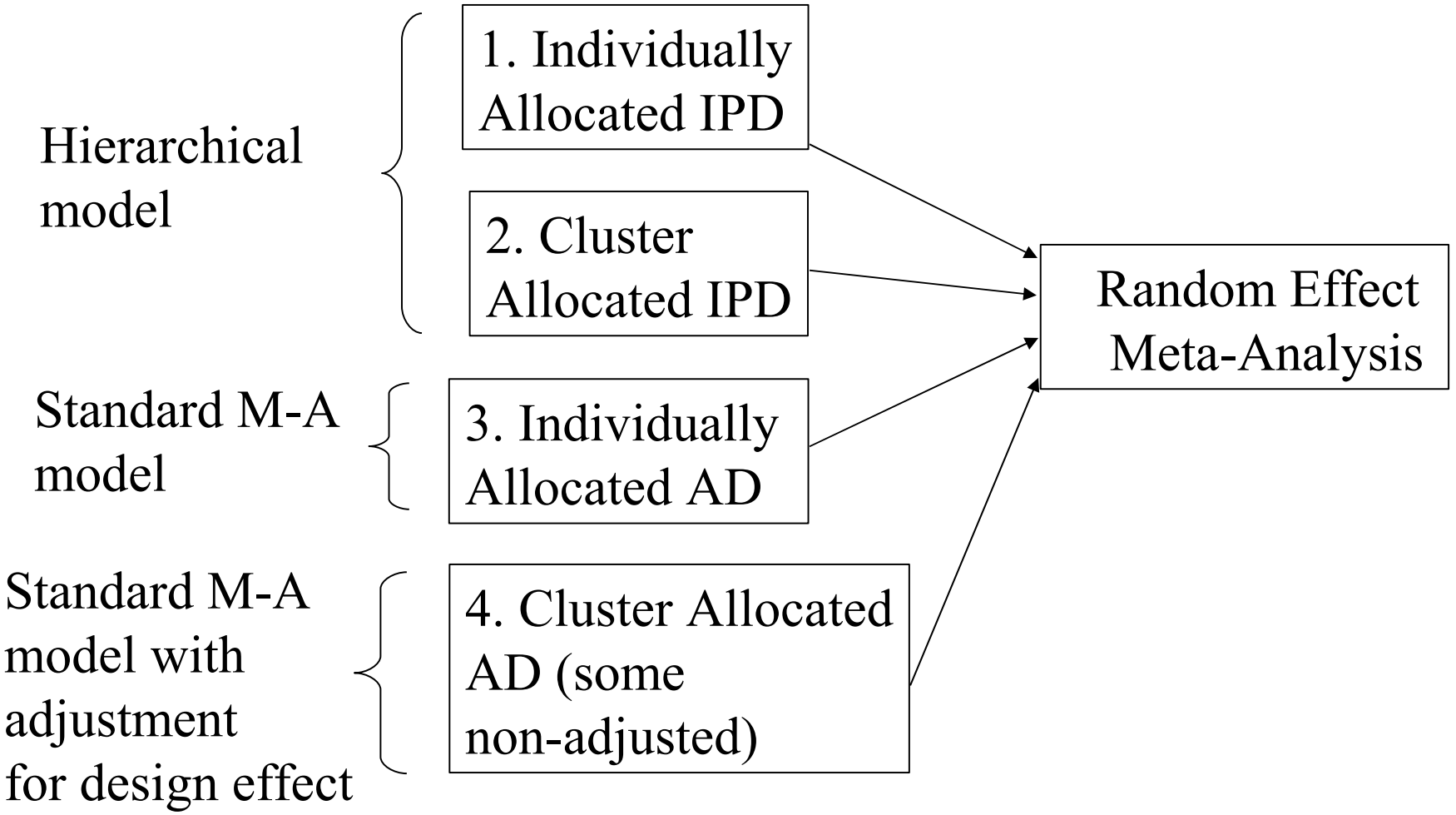
What can be done?

- Analyse at the level of the cluster; or
- Perform a more complex analysis that accounts for intra-class correlation
  - With IPD
    - » use, e.g., a mixed (multilevel) model
  - With AD
    - » can increase the variance of the study's effect estimate by multiplying by an estimate of the design effect
    - » or reduce its sample size to an effective sample size by dividing by an estimate of the design effect

Schematic of IPD meta-analysis of individual and cluster allocated studies



Schematic of the study/data types to combine

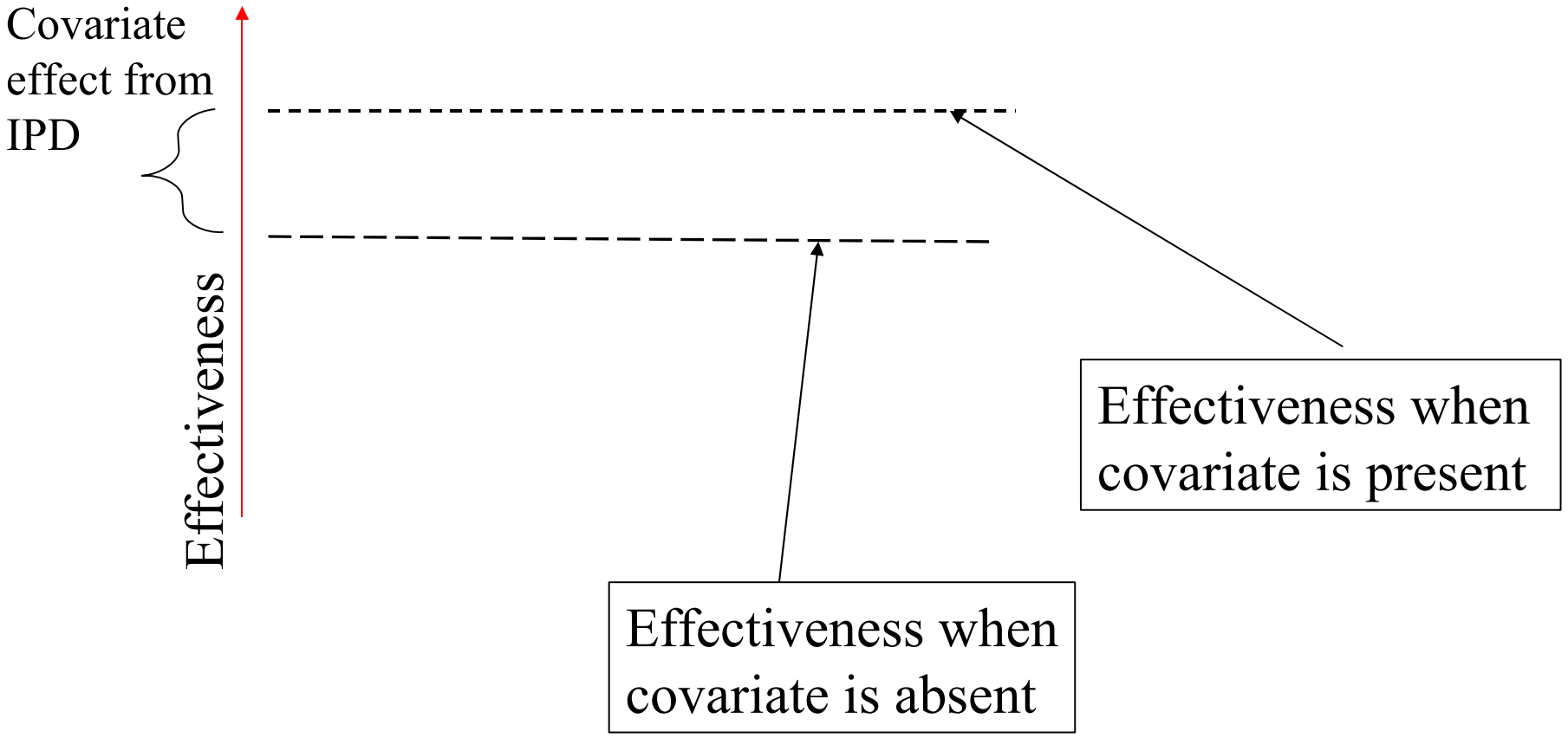


Adding In Covariates

- A mixture of individual level and study level, e.g.
  - Single parent family (yes/no)
  - *Subject level with IPD*

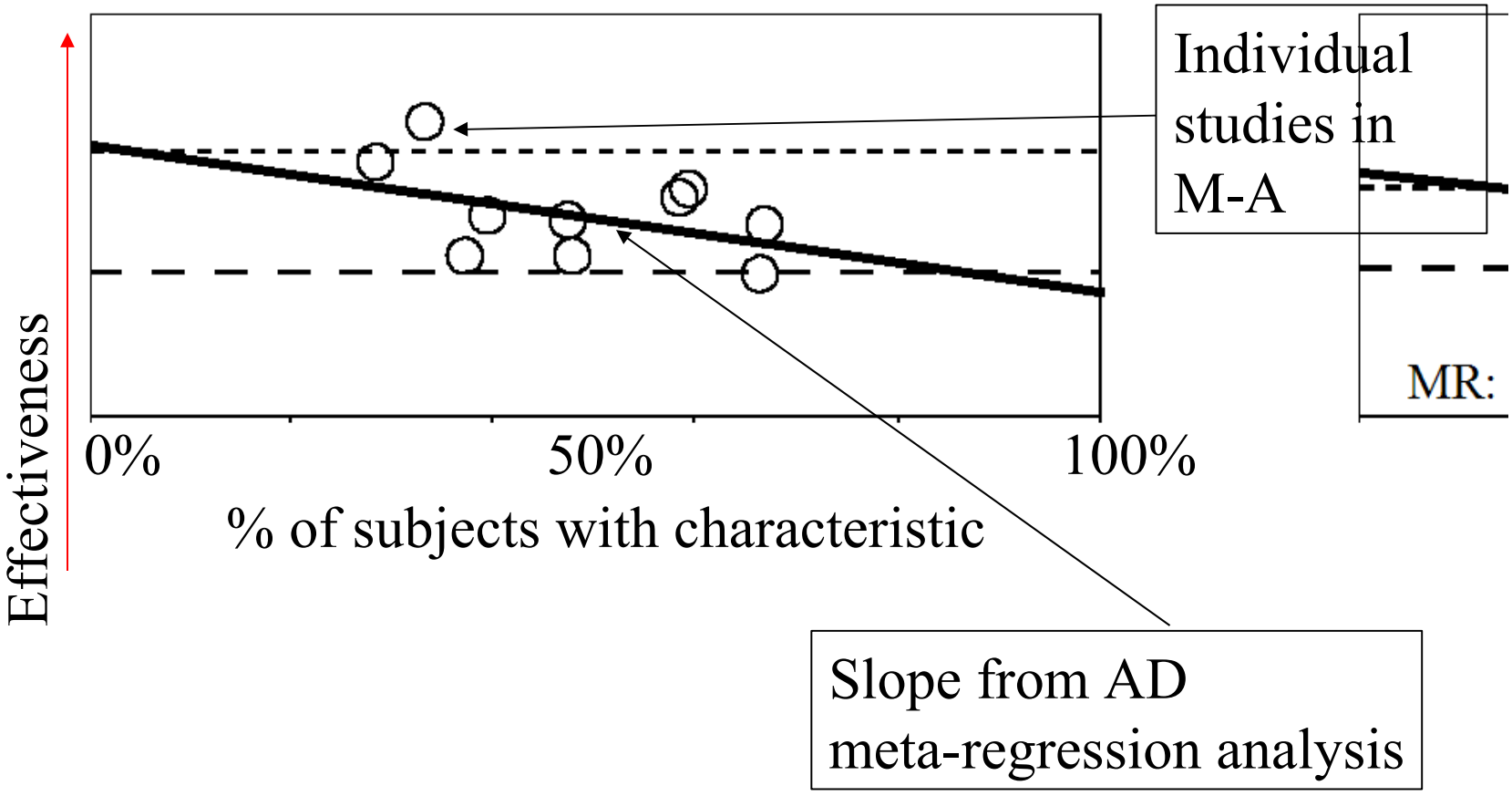
    &
  - % Participants single parents
  - *Study level with AD*

Estimating covariate effect using IPD



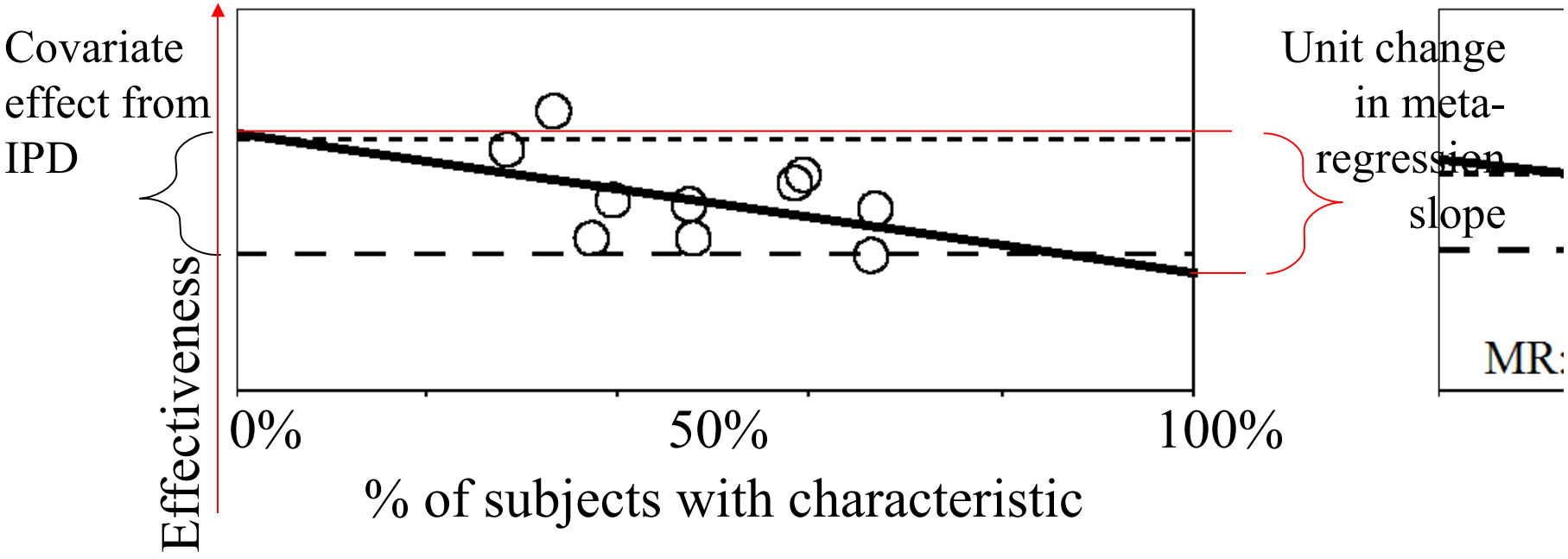
Placing a covariate effect & a treatment covariate interaction in the IPD models, can estimate the effect of covariate on intervention

Estimating covariate effect from AD

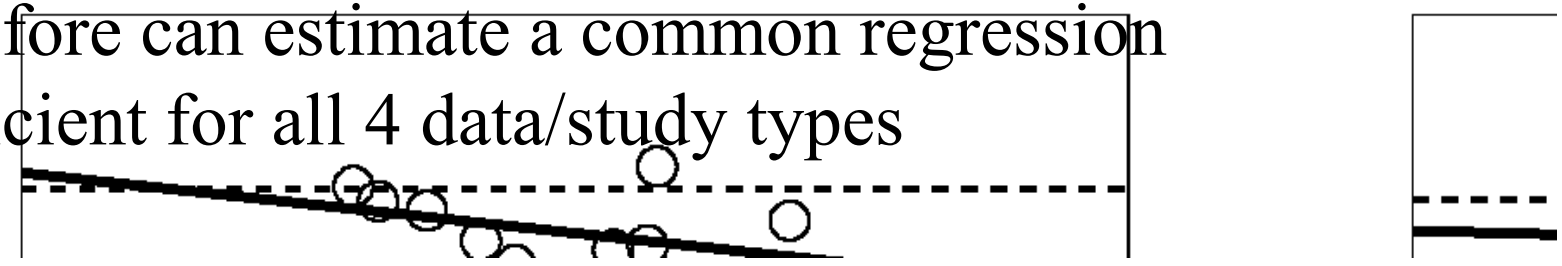


This is “standard” meta-regression where one slope is estimated across all studies

Reconciling estimates from IPD and AD



- IPD & AD estimate the same quantity if aggregate is a percentage (as a decimal) of people with binary trait(!)
- Therefore can estimate a common regression coefficient for all 4 data/study types



Example Results – Thermal Injuries

Social variables	*Safe hot tap water temperature*	*Keeping hot drinks out of child's reach*	*Possession of functioning smoke alarm*	*Possession of fitted and used fireguard*	*Possession of fire extinguisher*	*Safe storage of matches*
	Odds ratios for having each safety practice (95% CI)					
Gender						
Boys	0.82, 1.14 , 1.56 P=0.21	0.51, 0.81, 1.27 P=0.32	0.32, 2.31, 40.6 P=0.47	0.69, 0.88, 1.12 P = 0.002	0.50, 1.15, 2.66 P=0.29	Not calculable due to small sub group numbers
Girls	1.00, 1.47, 2.2	0.61, 0.92, 1.43	0.33, 2.35, 41.0	1.13, 1.46, 1.88	0.20, 0.67, 2.19	Not calculable due to small sub group numbers
Ethnic group						
Black and minority ethnic groups	0.34, 1.09, 2.69 P=0.41	0.51, 1.05, 2.14 P=0.29	0.83, 2.96, 12.88 P=0.32	0.33, 1.28, 4.66 P=0.45	Not calculable only measured by one study	0.54, 1.78, 6.64 P=0.10
White	0.31, 0.97, 2.57	0.54, 0.82, 1.25	0.80, 2.39, 10.15	0.34, 1.34, 4.31	Not calculable only measured by one study	0.13, 0.53, 1.88
Family type						
Single parent family	0.56, 1.51, 3.76 P=0.29	0.21, 0.91, 3.81 P=0.48	0.93, 2.92, 10.99 P=0.40	0.91, 1.33, 1.92 P=0.28	0.33, 2.86, 38.18 P=0.29	Not calculable due to small sub group numbers
Two parent family	0.51, 1.17, 2.35	0.60, 0.88, 1.29	1.07, 3.12, 11.39	0.99, 1.18, 1.39	0.65, 1.40, 2.94	Not calculable due to small sub group numbers
Housing tenure						
Resides in rented accommodation	1.72, 2.83, 4.66 P=0.03	0.47, 0.84, 1.52 P=0.45	0.59, 1.89, 7.36 P=0.42	0.77, 1.33, 2.13 P=0.14	-	-
Does not reside in rented accommodation	1.05, 1.56, 2.47	0.56, 0.81, 1.14	0.54, 1.81, 6.91	0.65, 1.12, 1.69	-	-

Discussion points

- Allows “all” data to be used “efficiently” and “appropriately”
- In regression, AD studies will usually not contribute as much information compared to if IPD were available
  - If availability of IPD is related to outcomes, then may be biased (but less so than just an IPD analysis)
- There are lots of potential model subsets
  - E.g. using parts 1, 2 and 5 could combine cluster and single allocated IPD only
- Lots of potential model variants
  - E.g. Add in baseline adjustments in the non-randomised studies (some before & after studies also exist)
- With 70+ outcomes in review, much slower than options 1 and 2 in STATA!!

Discussion points (cont.)

- Promoting a “Lego Bricks” approach to evidence synthesis
- Useful in many contexts
  - E.g. combining observational studies with different designs (matched/unmatched etc)
  - Multiple and indirect treatment comparisons
  - Comprehensive decision modelling

Further Work

- Intend to examine what gains were made in using this approach over more standard methods (i.e. just AD or just IPD etc)

- Can we create a decision model from the AD analysis informing when it would be cost effective to collect IPD compared with conducting new research?

Part 1: Model for individually allocated IPD studies

$$Y_{ij} \sim \text{Bernoulli}(p_{ij})$$

$$\text{logit}(p_{ij}) = \mu_j + \delta_j treat_{ij}$$

$$\mu_j \sim Normal(0, 10^6)$$

$i = 1, 2, \ldots, $ *Number of subjects in the jth individually allocated IPD study*

$j = 1, 2, \ldots, $ *Number of individually allocated IPD study*

Model described by Turner et al. (2000)

Part 2: Model for cluster allocated IPD studies

$$Y_{ikj} \sim \text{Bernoulli}(\, p_{ikj}\,)$$

$$\text{logit}(p_{ikj}) = \mu_{kj} + \delta_j treat_{ikj}$$

$$\mu_{kj} \sim Normal(\psi_j, \tau.cluster_j^2)$$

$$\psi_j \sim Normal(0, 10^6)$$

$$\tau.cluster_j \sim Uniform(0, 0.1)$$

i = 1, 2, . . . , *Number of subjects in the kth cluster of the jth cluster allocated IPD study*

k = 1, 2, . . . , *Number of clusters in the jth study*

j = (*Number of individually allocated IPD studies + 1), ... ,*
(Number of individually allocated IPD studies + Number of cluster allocated IPD studies)

Part 3: Model for individually allocated AD studies

$$r_{Cj} \sim Binomial(p_{Cj}, n_{Cj})$$

$$r_{Tj} \sim Binomial(p_{Tj}, n_{Tj})$$

$$\text{logit}(p_{Cj}) = \lambda_j$$

$$\text{logit}(p_{Tj}) = \lambda_j + \delta_j$$

$$\lambda_j \sim Normal(0, 10^6)$$

j = (Number of individually allocated ISLD studies + Number of cluster allocated IPD studies + 1) , ... , (Number of individually allocated ISLD studies + Number of cluster allocated IPD studies + Number of individually allocated AD studies)

Model described by Smith et al. (1995)

Part 4: Model for cluster allocated AD studies

$$design.effect_j = 1 + (ave.cluster.size_j - 1) \times icc_j$$

$$\sigma.adjusted_j^2 = \sigma_j^2 \times design.effect_j$$

$$T_j \sim \mathrm{N}(\delta_j, \sigma.adjusted_j^2)$$

$$icc_j \sim Normal(0, 0.0025) I(0,)$$

Example, (could be different for every j etc)

j = (Number of individually allocated IPD studies + Number of cluster allocated IPD studies + Number of individually allocated AD studies + 1), ... ,
(Number of individually allocated IPD studies + Number of cluster allocated IPD studies + Number of individually allocated AD studies + Number of cluster allocated AD studies)

Part 5: Model for combining all estimates of intervention effect from the 4 data sources

$$\delta_j \sim N\left(d, \tau^2\right)$$

$$d \sim Normal(0, 10^6)$$

$$\tau \sim Uniform(0, 0.1)$$

j = 1 . . . . . , (Number of individually allocated IPD studies + Number of cluster allocated IPD studies + Number of individually allocated AD studies + Number of cluster allocated AD studies)

Model Changes Required To Add A Covariate

Part 1: Model for individually allocated IPD studies

$$\text{logit}(p_{ij}) = \mu_j + \delta_j treat_{ij} + \beta_{0j}\, x_{ij} + \beta\, treat_{ij} x_{ij}$$

$$\beta_{0j} \sim Normal(0, 10^6)$$

Part 2: Model for cluster allocated IPD studies

$$\text{logit}(p_{ikj}) = \mu_{kj} + \delta_j treat_{ikj} + \beta_{0j}\, x_{ikj} + \beta\, treat_{ikj} x_{ikj}$$

$$\beta_{0j} \sim Normal(0, 10^6)$$

Part 3: Model for individually allocated AD studies

$$\text{logit}(p_{Tj}) = \lambda_j + \delta_j + \beta x.agg_j$$

Part 4: Model for cluster allocated AD studies

$$T_j \sim \text{N}(\delta_j', \sigma.adjusted_j^2)$$

$$\delta_j' = \delta_j + \beta x.agg_j$$

Part 5: Model for combining all estimates of intervention effect from the 4 data sources

$$\beta \sim Normal(0, 10^6)$$

• Hence all 4 study types “correctly” modelled to provide a log odds ratio to combine using a standard random effect meta-analysis model

•WinBUGS code is a “direct translation” of the model algebra

• Without covariates, this may seem excessive since we could have analysed each study separately and done a standard AD meta-analysis

. . . . . but

• We are interested in subject level covariates, so much power would be lost if we reduced ISLD covariates to summary level ones.

Models Developed

STAGE 1

- Combining IPD from cluster and non-cluster trials & AD cluster and non-cluster
  - Adjusting for unknown ICCs in cluster trials where only summary data was available

STAGE 2

- Incorporating patient level characteristics (at the individual and study level) into the model

Aside regarding study design

- How many clusters makes a trial?
  - E.g. populations of 2 islands randomised to intervention or nothing
  - i) Is this a trial? Would it make a difference if allocation was not random?
  - ii) Should it be adjusted for clustering even though it is impossible to estimate clustering effect from IPD of this study??
    - Randomly removed proportion of IPD appropriate for estimated design effect
  - iii) If we include non-randomised comparison studies of 2 populations should we always adjust these as a 2 cluster study???

External adjustments for AD clustering

- Evidence suggests effect is related to level of cluster
  - E.g. ICC for family clusters will probably be larger than those for health authority/city etc
  - We have at least 18 different cluster definitions (!)
    - Grouped into 5 levels we are considering as similar
    - Making different adjustments for these 5 levels based on IPD, if available, or published ICCs for similar levels if not
    - Adjustments are specified stochastically in WinBUGS