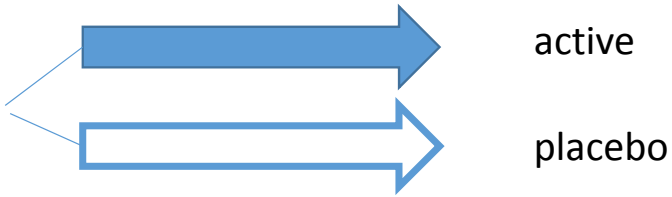
Meta-analysis combining parallel and cross-over trials

Francois Curtin

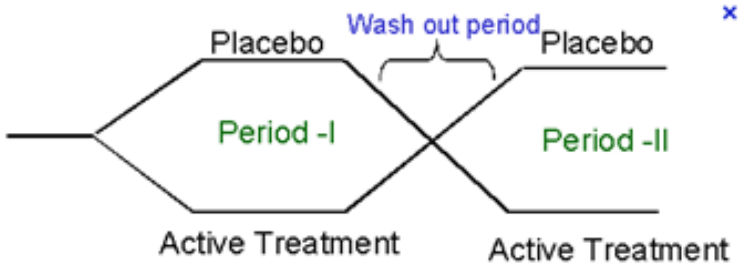
University of Geneva, Geneuro SA

Parallel trials



- The parallel trial design is considered as the trial design of reference in phase 3 (ICH guideline Statistical Principle for Clinical Trials E9).
- Design is simple with minimal biases
- The parallel approach is unavoidable for certain types of treatment or conditions:
  - trials assessing long-term treatments or endpoints having a definitive aspect, such as surgical intervention or an endpoint such as death
- Statistically, the evaluation of treatment effect in parallel trials is based on the **between-patient** comparison.
  - This represents the main drawback of the design:
  - the variation between patients' clinical status and between their treatment responses, translated statistically into the between-patient variance, may be large
  - thus this design may necessitate large sample size

Cross-over trials



Crossover design

- In a cross-over trial:
- Every subject/patient acts as his/her own control,
- One eliminates the between-patient variation
- Advantages:
  - To obtain the same number of observations, **fewer patients** have to be recruited
  - To obtain the same precision in estimation, **fewer observations** have to be obtained
- Major statistical advantage: each subject is used as his/her own control in the analysis, **removing the between-patient variance σ_b^2 (**of the endpoint of interest)

- only the within-patient variance component, noted σ_W^2, is used in the statistical analysis.
  - It is usually assumed that:

$$\sigma_W^2 < \sigma_b^2$$

A drawback of the cross-over is the risk of **carry-over,** i.e. the possibility that an intervention given in the second period or later is "contaminated" by the intervention given during the first period

The problem

- About 20% of Cochrane systematic reviews include cross-over trials (Lathyris et al 2007)
- However the combination of the information coming from the cross-over trial design in the metas is far from optimal:
  - either one uses the first period data only(one gets rid of half of the information),
  - or one analyses cross-over results as if they were parallel trials (Elbourne et al 2002): an analysis based on the between-patient variance, not efficient.
- Major hurdles to include cross-over trials into meta-analyses:
  - The difficulties arising from the **combination of different statistical metrics** according to the trial design
  - The problematic of **carry-over bias** inherent to the cross-over trials

Main assumption

- To combine different trial designs, the fundamental assumption is that these trials evaluate all **the same treatment** effect.
- In parallel trials, one usually estimates the difference between the population average responses, i.e. **marginal mean responses**, obtained in the treatment groups.
- In cross-over trials, to estimate the treatment effect in the cross-over design, one has 2 different ways of analysis:
- one can use a **marginal approach**
  - based on the generalized estimating equation (GEE), analogous to the analysis of parallel trials, which allows the introduction of the **correlation between observations**;
- or one can apply approaches such as the **random effects or subject-specific models**, see for example Ezzet and Whitehead, (1991)

- But the signification of the treatment effect, and the value of the treatment parameters, may differ if the analysis follows the **margina**l model or a s**ubject-specific model**, if the response distribution is not Normal or log-Normal (e.g Gail et al., 1984). – this may be an issue for combination in a meta

Simple model: Normal endpoints

A simple approach : Normal endpoints

Parallel trials:

- In the parallel design, the treatment effect is the difference of the mean outcomes in the treatment (T) and control (C) arms:

$$\overline{Y}_P = \overline{y}_T - \overline{y}_C$$

- The variance estimator is:

$$V_P = \left(\frac{n_T + n_C}{n_T n_C} \right) s^2,$$

- where s^2 is the pooled within treatment group variance and is calculated independently for each trial (n. = number of patients)

Normal endpoints in cross-over trials

Simple AB/BA Cross-over trials :

- Using an average cross-over difference which adjusts for period effect, the average treatment effect is defined as:

$$\bar{Y}_{XO} = \bar{d}_{XO} \qquad \bar{d}_{XO} = (\bar{d}_{AB} + \bar{d}_{BA})/2$$

- $\bar{d}_{AB}$ $\bar{d}_{BA}$ are the within patient treatment effect estimated in each sequence AB and BA
- An estimate of the variance of is:

$$V_{XO} = \frac{1}{4}\left(\frac{n_{AB} + n_{BA}}{n_{AB}\, n_{BA}}\right) s_x^2$$

- where s^2_x is the cross/over difference variance obtained from the 2 sequences of the XO trial.

Meta formula to combine both designs

- Simple approach: pooling results from the 2 designs
- The estimate of the treatment effect is the weighted average of estimates obtained in the 2 trial designs

$$\overline{Y}_{\text{Meta-Combined}} = \frac{\sum_{\text{Parallel}} W_P \overline{Y}_P + \sum_{\text{Crossover}} W_{XO} \overline{Y}_{XO}}{\sum_{\text{Parallel}} W_P + \sum_{\text{Crossover}} W_{XO}}$$

- And the variance estimate is given by (where weights w. = 1/v. , inverse of variance):

6)

$$\frac{1}{\sum_{\text{Parallel}} W_P + \sum_{\text{Crossover}} W_{XO}}$$

- …a very classical approach!

Trickier situation: Non-normal endpoints

More tricky with binary endpoints

- Let's look at binary endpoints
- Usually one will use odds ratios (OR) to analyse the results, in particular for a meta-analysis
- For **parallel studies**, the results can be presented in classical 2x2 Tables, and for a given trial, the maximum likelihood estimate (MLE) or Mantel-Haenszel OR is the cross-product:

$$OR_{MH\text{-}P} = ad/bc$$

	Treatment	No treatment
Success	a	b
Failure	c	d

- where a, b, c, d are the cell entries and a + b + c + d = N, the total number of subjects.
- The usual variance estimate of the logarithm of this OR is:

$$var(\ln OR_{MH\text{-}P}) = 1/a + 1/b + 1/c + 1/d$$

In a cross-over, discordant pairs are important

3.1.b

Sequence AB

	Period 1	
	1	0
Period 2		
1	W_{AB}	X_{AB}
0	Y_{AB}	Z_{AB}

Sequence BA

	Period 1	
	1	0
Period 2		
1	W_{BA}	X_{BA}
0	Y_{BA}	Z_{BA}

One looks at pairs with discordant responses to treatments

Odds ratios for cross-over trials

- For **cross-over trials**, the Mantel-Haenszel OR is the ratio of the numbers of discordant pairs (Breslow and Day, 1980).
- In each of the 2 sequences of the cross-over trial, the sum of pairs of discordant responses to treatment (A=0, B=1) is $x_{AB} + y_{BA}$; and the sum of pairs of discordant responses to treatment (A=1, B=0) is $x_{BA} + y_{AB}$.
- Consequently the OR is:

$$OR_{MH\text{-}XO} = (y_{AB} + x_{BA})/(x_{AB} + y_{BA})$$

and the variance estimate of the logarithm of this OR is:

$$var(\ln OR_{MH\text{-}XO}) = 1/(x_{AB} + y_{BA}) + 1/(y_{AB} + x_{BA})$$

Need to combine marginal OR

- However the cross-over Mantel Haeszel OR is a **conditional OR** which carry a different information from the OR computed in parallel trial
- Thus it **cannot** be combined with the marginal OR computed in parallel trials
- To combine the results, one needs to combine marginal OR obtained in cross-over trials with marginal OR obtained in parallel trials - main assumption of similar metrics

Need for marginal OR for cross-over trials

- The **marginal method** uses the probabilities of success or failure in periods 1 or 2 calculated without taking into account the results of the other period.
  - The marginal cross-over OR estimator is equivalent to the MLE or Mantel Haenszel OR estimator of parallel trials
- The notation for the marginal probabilities is given in Table below: those are the probabilities of a given result when a given drug is administered
- Becker and Balagtas (1993) proposed a model for marginal logits obtained from cross-over trials. The sum of the marginal probabilities over periods is used to calculate the MLE of the OR equation :

Computation of the marginal probabilities of success/failure according to treatment

3.1.b

Sequence AB

	Period 1: 1	Period 1: 0
Period 2: 1	w_{AB}	x_{AB}
Period 2: 0	y_{AB}	z_{AB}

Sequence BA

	Period 1: 1	Period 1: 0
Period 2: 1	w_{BA}	x_{BA}
Period 2: 0	y_{BA}	z_{BA}

3.1.c

Marginal probabilities	Estimators	
$p_{1+} = \sum_{Periods} Prob(Y = 1 \mid treatment = A)$	n_{1+}/N	where $n_{1+} = w_{AB} + y_{AB} + w_{BA} + x_{BA}$
$p_{2+} = \sum_{Periods} Prob(Y = 0 \mid treatment = A)$	n_{2+}/N	where $n_{2+} = x_{AB} + z_{AB} + y_{BA} + z_{BA}$
$p_{+1} = \sum_{Periods} Prob(Y = 1 \mid treatment = B)$	n_{+1}/N	where $n_{+1} = w_{AB} + x_{AB} + w_{BA} + y_{BA}$
$p_{+2} = \sum_{Periods} Prob(Y = 0 \mid treatment = B)$	n_{+2}/N	where $n_{+2} = y_{AB} + z_{AB} + x_{BA} + z_{BA}$
$p_{11} = Prob((Y,Z)=(1,1))$	n_{11}/N	where $n_{11} = w_{AB} + w_{BA}$
$p_{22} = Prob((Y,Z)=(0,0))$	n_{22}/N	where $n_{22} = z_{AB} + z_{BA}$

*1 = success, 0 = failure.

Computation of the marginal odds ratio

$$OR_{BB} = \frac{p_{1+}\, p_{+2}}{p_{2+}\, p_{+1}} = \frac{n_{1+}\, n_{+2}}{n_{2+}\, n_{+1}}$$

- A variance estimator for this (log) OR, which decreases when the between-period correlation increases :

  $\text{var}(\ln OR_{BB}) = (1/p_{1+} + 1/p_{2+} + 1/p_{+1} + 1/p_{+2} - 2\Delta)/N$

- where

  $\Delta = (p_{11} - p_{1+}p_{+1})/(p_{1+}p_{+1}p_{2+}p_{+2})$

- and p_{11} is the joint probability of success in the two periods .

Variance of the marginal crossover OR

- The term Δ/N is **a covariance** and can be rewritten:

$$\Delta/N = \rho/[N(p_{1+}p_{+1}p_{2+}p_{+2})^{1/2}]$$

- where

$$\rho = (p_{11} - p_{1+}p_{+1})/(p_{1+}p_{+1}p_{2+}p_{+2})^{1/2}$$

- is the **binary correlation coefficient** of the 2x2 table (Bishop et al., 1975) – the correlation of the observations in the cross-over trial...

- This OR will be the one to be used in the combined meta

Relationship between conditional and marginal OR

- Why can't we combine marginal and conditional OR?
- According to the magnitude of the binary correlation, the 2 OR (marginal and conditional) estimates have not the same values.
- The joint conditional OR estimators are related to the marginal OR estimators by a factor g:

$$OR_{Marginal} = g\ OR_{Conditional}$$

- g is given by:

$$g = \frac{\rho\sqrt{\frac{p_{+2}\,p_{1+}}{p_{+1}\,p_{2+}}} - 1}{\rho\sqrt{\frac{p_{+1}\,p_{2+}}{p_{+2}\,p_{1+}}} - 1} = \frac{\rho\sqrt{OR_{Marginal}} - 1}{\rho\sqrt{1/OR_{Marginal}} - 1}$$

- with $\rho = 0$, $g = 1$ and with $\rho > 0$, $g < 1$, assuming $OR > 1$.

Only marginal OR can be pooled in combined design meta

- Then the combination can follow the classical formula for weighted average as defined for the continuous endpoint

$$\ln(OR_{BB\text{-Combined}}) = [\sum_{Parallel} w_P \ln OR_{MH-P} + \sum_{Crossover} w_{BB} \ln OR_{BB}]/[\sum_{Parallel} w_P + \sum_{Crossover} w_{BB}]$$

- where, for each trial in each design,

$w_P = 1/var(\ln OR_{MH\text{-}P})$ $w_{BB} = 1/var(\ln OR_{BB})$.

Simple meta with 5 trials on protein diet

Table 3.2. Response of renal function to normal or low protein diet. Results, odds ratios and between-period correlations for cross-over (a) and parallel (b) trials.

a. Cross-over trials

	Number of subjects by outcome				OR BB (95% CI)	OR MH (95% CI)	Correlation
	Improved with both treatments	Improved w. low Protein, deteriorated w. normal diet	Improved w. normal Diet, deteriorated w. low protein	Deteriorated w. both treatment			
Barsotti et al 1988	0	5	0	3	13.5 (1.2 to 152.1)	11.0 (0.6 to 198.9)	0.0
Walker et al 1989	3	7	0	9	4.7 (1.5 to 14.4)	15.0 (0.9 to 262.6)	0.4

b. Parallel trials

	Number of subjects by outcome				OR MH (95% CI)
	Low protein diet		Normal diet		
	Improved	Deteriorated	Improved	Deteriorated	
Ciavarella et al 1987	6	1	1	8	48.0 (2.5 to 930.8)
Zeller et al 1991	10	10	3	12	4.0 (0.9 to 18.8)
Dullart et al 1993	10	4	8	8	2.5 (0.5 to 11.5)

*calculated with a correction of 0.5 for each cell in cross-over trials. BB: Becker Balagtas, MH: Mantel Haenszel.

Combination of OR according to different methods across cross-over, parallel and all trials assessing the effect of reduced protein diet on the renal function.

		lnOR	variance	OR	95%confidence interval
Mantel-Haenszel	Cross-over	2.56	1.08	13.0	1.69 to 99.20
	Parallel	1.52	0.24	4.58	1.75 to 11.94
	Combined	1.84	0.18	6.27	2.74 to 14.46
Becker-Balagtas	Cross-over	1.73	0.27	5.63	2.03 to 15.66
	Parallel	1.47	0.27	4.36	1.57 to 12.01
	Combined	1.60	0.14	4.95	2.41 to 10.18

The carry-over issue

Carry-over effect

- The problem of carry-over (persisting effect of a treatment given before) is a crucial issue in the analysis of cross-over trials and consequently in meta including this design.
  - Drug with a long persistence in the body and washout period between the two periods of Xotrial are too short
- A common practice is to analyse only the first period of the XO trials (**First** analysis) and include only these results.
- But this may lead to a **biased subset of trials** in a meta and it is a less efficient treatment estimate.
- Assuming that cross-over trials are performed only when the carry-over seems unlikely, systematically rejecting the second period of the cross-over trials is very conservative

Carry-over effect

- When including cross-over trials in a combined-design meta-analysis, one may be tempted to introduce selectively cross-over results either analysed by **First** or analysed with the 2 period results on the basis of information about carry-over.
- This is a repetitive application of the **2-stage test** used in cross-over trials which first tests for carry-over and then accordingly estimates treatment effect either based on the first period or based on the 2 periods.
- The **2-stage test has been shown to be misleading**, principally because of the correlation existing between the carry-over estimator and the estimator based on first period analysis. This should be avoided.

Carry-over effect

- In practice:
- If the information is available, a meta-analysis should be computed **either with data from the two cross-over periods or only with the data from the first period**, but a mixture of the two approaches should be avoided.
- There is no definitive answer to the question of including or not the second period of cross-over trial in a combined design meta-analysis.
  - The choice between the risk of bias and the benefit of an increased precision depends on the questions the meta-analysis aims to address
- As long as detailed information on sequence is available, one can recommend to perform **2 analyses 1) based on the First XO period and 2) one based on estimators including both periods.**
- The most suitable approach is to present both estimates and to discuss the results.
  - One can be more interested by a minimally biased estimate of the treatment effect in order to draw some conclusion about its absolute value.
  - Conversely, if one seeks to demonstrate the superiority of a new treatment in a statistically significant way, a bias (towards the null) in the meta-analysis estimate is less important, because in this case both treatment effect and variance matter. In this case results from both periods should be privileged.

Extending the model

Extending the model

- There is a need to extend these methods to cross-over trials including more than two periods and two treatments (higher order cross-over trials) and to consider other outcome distributions.
- the idea is to use of the **generalized estimating equations (GEE)** to pool results of parallel and cross-over trials in meta-analyses
- The GEE allows longitudinal analysis according to the **marginal model** and is well suited to the population averaged interpretation of meta-analysis including cross-over studies.
- It allows also to pool the results of **cross-over trials of higher order,** i.e. cross-over trials with more than two sequences or two periods
- The repeated observations (clusters) are the average responses of the repeated treatment groups (cluster of 1 for parallel, of 2 or more for XO trials)
- It may allow to **include a variable to correct for the carry-over**
- **The weights (inverse variance) are those observed in the treatment group responses and no longer the contrast variances**

GEE approach: the formulas

- In GEE, a function h links covariates $\mathbf{x_s}$ to the marginal expectation of the outcome $\mathbf{Y}_s$:
  - $E(\mathbf{Y}_s) = \mu_s = h(\mathbf{x_s}\beta)$
- and a function g relates the expectation of the outcome to its variance v_s :
  - $v_s = v(\mathbf{Y}_s)\phi = g(\mu_s)\phi$
- where $v(\mathbf{Y}_s)$ is the variance function and ϕ is a scale parameter.
- To estimate β, one solves the estimating equation,

$$U(\boldsymbol{\beta}) = \sum_{s=1}^{n} \left(\frac{\partial \boldsymbol{\mu}_S}{\partial \boldsymbol{\beta}}\right)^T \mathbf{V}_S^{-1}\left[\mathbf{Y}_S - \boldsymbol{\mu}_S(\boldsymbol{\beta})\right] = 0$$

- where the summation is over the n clusters, $\mathbf{V}_s$ is the **matrix of variance-covariance** within clusters and $\mathbf{Y_s}$ is the vector of n_s observations for each cluster.
- The matrix $\mathbf{V}_s$ can be written:

$$\mathbf{V}_s = \mathbf{A}_s\mathbf{R}_s(\alpha)\mathbf{A}_s \qquad (1)$$

- where the n_s x n_s matrix $\mathbf{A}_s$ = diag($v(Y_{s1})$,…$v(Y_{sn_s})$) includes the variance functions, $\mathbf{R}_s(\alpha)$ is a correlation matrix and α is the within cluster correlation.

Adaptation of GEE to include trial variance data

- Here for each trial, the average outcome of each treatment group is **weighted by the inverse of its sample variance**. Weights are in matrix $\mathbf{W}_{ij}$ defined as:

$$\mathbf{W}_{ij} = \mathrm{diag}(w_{i1}^{1/2} ,\ldots w_{in_i}^{1/2}) = \mathrm{diag}(\mathrm{var}(\bar{y}_{i1})^{-1/2} ,\ldots, \mathrm{var}(\bar{y}_{in_i})^{-1/2})$$

- In equation (1), $\mathbf{R}_{ij}(\alpha)$ include the correlations observed in cross-over trials:

$$\begin{pmatrix} 1 & r_{12} & . & r_{1q} \\ r_{21} & 1 & . & . \\ . & . & . & . \\ r_{q1} & . & . & 1 \end{pmatrix}$$

- where $r_{\cdot\cdot}$ are the between period cross-over correlation coefficients obtained from the original trial reports.
- In equation (1), matrix $\mathbf{V}_{ij}$ can be written ($\mathbf{A}_{ij} = \mathbf{I}$ if outcomes are Normal):

$$\mathbf{V}_{ij} = \mathbf{W}_{ij}^{T} \mathbf{A}_{ij} \mathbf{R}_{ij} \mathbf{A}_{ij} \mathbf{W}_{ij} = \mathbf{W}_{ij}^{T} \mathbf{R}_{ij} \mathbf{W}_{ij}$$

Meta on hypertension treatment: 14 parallel and 13 cross-over trials

Table 1. Randomized trials assessing the effect of sodium reduction on blood pressure

	Design	Sample size contrl	trtmt	DBP control grp Mean	s.d.	DBP treatmt grp mean	s.d.	Treatmt effect	Variance Effect	Variance (cor=0.5)	Corr.	A
Morgan, 1978	parallel	31	31	99	8.4*	92	8.4*	-7.0	4.6	.	.	>
Costa, 1981	parallel	20	21	83.9	11.0	78.1	9.0	-5.8	9.9	.	.	
Morgan, 1981male	parallel	6	6	94.0	7.1*	87.0	7.1*	-7.0	16.8	.	.	
Morgan, 1981 fem	parallel	6	6	92.0	5.7*	89.0	5.7*	-3.0	10.8	.	.	
Puska, 1983	parallel	38	34	86.9	9.2	86.5	10.5	-0.4	5.4	.	.	
Silman, 1983	parallel	10	15	86.5	10.8*	80.9	10.8*	-6.6	19.5	.	.	
Erwteman, 1984	parallel	44	50	94.4	12.0	92.9	10.4	-1.5	5.5	.	.	
Fagerberg, 1984	parallel	15	15	94.6	7.4	90.5	9.3	-4.1	9.4	.	.	
Maxwell, 1984	parallel	18	12	78	7.6	80	7.6	2.0	8.0*	.	.	
Chalmers, 1986	parallel	52	48	93.3	4.5*	89.5	4.5*	-3.8	0.81	.	.	
Logan, 1986	parallel	37	38	91.7	5.2	91.5	5.2	-0.2	1.4	.	.	
ANHMRC a, 1989	parallel	53	50	94.6	6.6	91.4	4.9	-3.2	1.3	.	.	
Dodson, 1989	parallel	17	17	90.4	5.7	87.6	10.5	-2.8	8.4	.	.	
HPTRG, 1990	parallel	174	177	80.0	7.5*	80.2	7.5*	0.2	0.64	.	.	
Parijs, 1973	crossvr	15	15	112.3	15.1	115.5	12.5	3.3	18.7	13.0	0.22	
Skrabal, 1981	crossvr	20	20	73.1	9.8g	70.1	8.5g	-3.0	4.13*	4.2	0.5**	
McGregor, 1982	crossvr	19	19	97.0	8.7	92.0	8.7	-5.0	3.2	4.0	0.60	
Watt, 1983	crossvr	18	18	82.6	3.4*	82.3	3.4*	-0.3	0.64	0.64	0.5**	
Cooper, 1984	crossvr	113	113	60.7	10.0	59.3	11.0	-1.4	1.1	0.99	0.44	
Richards, 1984	crossvr	12	12	92.4	12.1	90.6	12.5	-1.8	12.6*	12.6	0.5**	
Watt, 1985 LL	crossvr	31	31	63.6	9.5	65.0	9.5	1.4	0.81	2.9	0.86	
Watt, 1985 HH	crossvr	35	35	63.3	11.2	64.5	11.2	1.2	0.86	3.6	0.88	
Grobbee, 1987	crossvr	40	40	73.3	9.5	72.5	9.5	-0.8	2.3*	2.3	0.5**	
ANHMRC b, 1989	crossvr	88	88	94	3.8*	92	3.8*	-2.0	0.16	0.16	0.5**	
Dodson, 1989	crossvr	9	9	92.4	10.0	87.3	6.7	-5.1	8.6	8.7	0.47	
McGregor, 1989	crossvr	20	20	100.0	8.9	95.0	8.9	-5.0	2.6	4.0	0.67	
Myers, 1989	crossvr	172	172	77.2	11.8	75.3	11.8	-1.9	0.81*	0.81	0.5**	

DBP: diastolic blood pressure, corr: correlation, s.d. standard deviation. LL subjects with parents in the botto third of age specific BP distribution, HH subjects with parent in the top of their age specific BP distribution. *value imputed, ** correlation fixed at 0.5

Table 2. Meta-analysis assessing the effect of sodium reduction on blood pressure. Treatment effect estimates by trial design according to different methods of meta-analysis.

Meta-analysis method	Effect	No of trials	Treatment estimate	Variance estimate
Weighted average	Treatment (parallel)	14	-1.99	0.18
	Treatment (cross-over)	13	-1.33	0.07
	Treatment (combined)	27	-1.52	0.05
GEE (B) original crossover correlation group variance weights	Treatment (parallel)	14	-1.65	0.18
	Treatment (cross-over)	13	-1.32	0.07
	Treatment (combined)	27	-1.42	0.05
GEE original cross-over correlation model including age covariate	Treatment (combined)	27	-0.42	0.11
	Age $\geq$ 50	27	11.66	0.16
	Interaction Treatment*age	27	-1.85	0.21

There may be a difference in weighting
As in the GEE, the weights are those obtained at the level of the treatment goup and not at the level of the contrasts

GEE allows to expand the possibility of combining results

- GEE allows to combine results based on a **marginal** estimation of the trial results from parallel and cross-over trial : combination is possible
- One integrate the weights of the trials as well as the correlation obtained in cross-over trials
- The technique allows to include cross-over trials which would have a more complex design than the simple AB/BA cross-over trial
- Endpoints following the distributions which can be modelled with the GEE can be easily combined by this method (exponential family distributions)
- Variables explaining the heterogeneity of the results can be included in the model

Regression methods allowing for random effects

- GEE permits the combination of different trial designs allowing for the introduction of:
  - the cross-over correlation
  - covariates according to a fixed effects model which can control at least for part of the heterogeneity
- Among clinical trials included in a meta-analysis, there are **variations in protocols, methods, assessment of endpoints, patient populations or trial designs**. These variations may yield differences in the treatment effect estimates
- If these differences cannot be adjusted or controlled, the heterogeneity of results suggests considering the treatment
  - not as the result of a fixed effect similar for all trials,
  - but rather as a **random treatment variable** with its own distribution: this is the random effects meta-analysis (DerSimonian and Laird, 1986).
- The use of different trial designs may well be a reflection of differences in the clinical settings compatible with the heterogeneity of treatment effect.

Random effects

- It is easily possible to introduce random effects in the regression analysis to account for the heterogeneity
- Iterative generalised least square (code in S+) or Bayesian MCMC methods (code BUGS/WinBUGS) can be used
- A hierarchical model is well suited(meta based on trial results):
  - First level : trial observations
  - Second level: meta-analytic parameters
  - Third level: priors
- Original sample variance can be used (semi-random effect) or new variances for the trial groups can be computed (fully random effect)

“Hierarchical” model for fixed effects

	Fixed effects
I. Observed data $\mathbf{Y}_i$	$\mathbf{Y}_i \mid \boldsymbol{\theta}_i \sim N(\boldsymbol{\theta}_i, \mathbf{V}_i)$
II. Unknown param. $\boldsymbol{\theta}_i$	$\boldsymbol{\theta}_i = \mathbf{X}_i\boldsymbol{\beta}_i$ $\boldsymbol{\beta}_i \mid \boldsymbol{\mu} \sim N(\boldsymbol{\mu}, \mathbf{0})$
III. Hyperpriors*	

Hierarchical model for semi-random effects (variance of treatment group observed)

	Semi-random effects
I. Observed data $\mathbf{Y}_i$	$\mathbf{Y}_i \mid \boldsymbol{\theta}_i \sim N(\boldsymbol{\theta}_i, \mathbf{V}_i)$
II. Unknown param. $\boldsymbol{\theta}_i$	$\boldsymbol{\theta}_i = \mathbf{X}_i\boldsymbol{\beta}_i$ $\boldsymbol{\beta}_i \mid \boldsymbol{\mu}, \boldsymbol{\Omega} \sim N(\boldsymbol{\mu}, \boldsymbol{\Omega})$
III. Hyperpriors*	$\boldsymbol{\mu} \mid \mathbf{a}, \mathbf{B} \sim N(\mathbf{a}, \mathbf{B})$ $\boldsymbol{\Omega}^{-1} \mid \mathbf{C}, p \sim W_p(\mathbf{C}, p)$

Sample variance observed in the trials is used in the semi-random effects model

Hierarchical model for fully random effects
(variance of treatment group is computed by the model)

	Fully random effects
I. Observed data $\mathbf{Y}_i$	$\mathbf{Y}_i \mid \boldsymbol{\theta}_i, \boldsymbol{\Sigma}_P, \boldsymbol{\Sigma}_X \sim N(\boldsymbol{\theta}_i, (1-I_X)\boldsymbol{\Sigma}_P + I_X\boldsymbol{\Sigma}_X)$
II. Unknown param. $\boldsymbol{\theta}_i$	$\boldsymbol{\theta}_i = \mathbf{X}_i\boldsymbol{\beta}_i$ $\boldsymbol{\beta}_i \mid \boldsymbol{\mu}, \boldsymbol{\Omega} \sim N(\boldsymbol{\mu}, \boldsymbol{\Omega})$
III. Hyperpriors*	$\boldsymbol{\mu} \mid \mathbf{a}, \mathbf{B} \sim N(\mathbf{a}, \mathbf{B})$ $\boldsymbol{\Omega}^{-1} \mid \mathbf{C}, p \sim W_p(\mathbf{C}, p)$

… as before
Meta on hypertension treatment: 14 parallel and 13 cross-over trials

Table 2. Randomized trials of sodium reduction

	Design	Sample size contrl	trtmt	DBP control grp mean	s.d.	DBP treatmt grp mean	s.d.	Treatmt effect	Variance Effect	Variance (cor=0.5)	Corr.	Age
Morgan, 1978	parallel	31	31	99	8.4*	92	8.4*	-7.0	4.6	.	.	>50
Costa, 1981	parallel	20	21	83.9	11.0	78.1	9.0	-5.8	9.9	.	.	24
Morgan, 1981male	parallel	6	6	94.0	7.1*	87.0	7.1*	-7.0	16.8	.	.	39
Morgan, 1981 fem	parallel	6	6	92.0	5.7*	89.0	5.7*	-3.0	10.8	.	.	39
Puska, 1983	parallel	38	34	86.9	9.2	86.5	10.5	-0.4	5.4	.	.	40
Silman, 1983	parallel	10	15	86.5	10.8*	80.9	10.8*	-6.6	19.5	.	.	56
Erwteman, 1984	parallel	44	50	94.4	12.0	92.9	10.4	-1.5	5.5	.	.	46
Fagerberg, 1984	parallel	15	15	94.6	7.4	90.5	9.3	-4.1	9.4	.	.	51
Maxwell, 1984	parallel	18	12	78	7.6	80	7.6	2.0	8.0*	.	.	48
Chalmers, 1986	parallel	52	48	93.3	4.5*	89.5	4.5*	-3.8	0.81	.	.	52
Logan, 1986	parallel	37	38	91.7	5.2	91.5	5.2	-0.2	1.4	.	.	47
ANHMRC a, 1989	parallel	53	50	94.6	6.6	91.4	4.9	-3.2	1.3	.	.	58
Dodson, 1989	parallel	17	17	90.4	5.7	87.6	10.5	-2.8	8.4	.	.	61
HPTRG, 1990	parallel	174	177	80.0	7.5*	80.2	7.5*	0.2	0.64	.	.	39
Parijs, 1973	crossvr	15	15	112.3	15.1	115.5	12.5	3.3	18.7	13.0	0.22	41
Skrabal, 1981	crossvr	20	20	73.1	9.8	70.1	8.5	-3.0	4.13*	4.2	0.5**	23
McGregor, 1982	crossvr	19	19	97.0	8.7	92.0	8.7	-5.0	3.2	4.0	0.60	49
Watt, 1983	crossvr	18	18	82.6	3.4*	82.3	3.4*	-0.3	0.64	0.64	0.5**	52
Cooper, 1984	crossvr	113	113	60.7	10.0	59.3	11.0	-1.4	1.1	0.99	0.44	16
Richards, 1984	crossvr	12	12	92.4	12.1	90.6	12.5	-1.8	12.6*	12.6	0.5**	36
Watt, 1985 LL	crossvr	31	31	63.6	9.5	65.0	9.5	1.4	0.81	2.9	0.86	23
Watt, 1985 HH	crossvr	35	35	63.3	11.2	64.5	11.2	1.2	0.86	3.6	0.88	22
Grobbee, 1987	crossvr	40	40	73.3	9.5	72.5	9.5	-0.8	2.3*	2.3	0.5**	24
ANHMRC b, 1989	crossvr	88	88	94	3.8*	92	3.8*	-2.0	0.16	0.16	0.5**	58
Dodson, 1989	crossvr	9	9	92.4	10.0	87.3	6.7	-5.1	8.6	8.7	0.47	62
McGregor, 1989	crossvr	20	20	100.0	8.9	95.0	8.9	-5.0	2.6	4.0	0.67	57
Myers, 1989	crossvr	172	172	77.2	11.8	75.3	11.8	-1.9	0.81*	0.81	0.5**	37

DBP: diastolic blood pressure, corr: correlation, s.d. standard deviation. LL subjects with parents in the bottom third of age specific BP distribution, HH subjects with parent in the top of their age specific BP distribution.
*value imputed, ** correlation fixed at 0.5

Table 4. Random effects meta-analysis according to DerSimonian and Laird, (R)IGLS and Bayesian methods.

	DerSimonian And Laird		RIGLS model 1	Bayes SemiR model 1	Bayes FullyR model 1'
Treatment effect	-1.81		-1.81	-1.80	-2.27
Variance	0.20		0.21	0.23	0.29
95%confidence int.	-2.69 to -0.93	-	-2.71 to -0.91	-2.74 to -0.86	-3.33 to -1.21
Between-study var.	2.41		2.65	2.50	6.04
var of BS variance				2.56	5.43

SemiR: semi-random, FullyR: fully-random, BS: between-study

First conclusions

- The introduction of random effects is of particular interest in combined design meta-analysis.
  - When different trial designs are used, one can expect that there may be significant **variation in the treatment** effect which justifies the use of a random effects model.
- With random effects metas, the **weights of trials become more homogenous,** so that the original trial variance and covariance have a lesser impact on the meta-analytic estimates.
- It **decreases the weights** of the cross-over design which have a high relative weight in combined design meta-analysis analysed by a classical weighted average method (Curtin et al, 2002a).
  - This is of importance if one considers the **potential risk of carry-over** bias associated with cross-over trials

First conclusions

- The interest of the regression model proposed with GEE and random effects extensions is notably the possibility to introduce a carry-over parameter to control for this bias.
- “Fully Bayesian” models may present advantages: the Bayesian approach permits the calculation of the exact variance from the posterior distributions of parameters (Brown and Prescott, 1999), which can be of value to circumvent the limitations in the estimation of standard errors of cross-over trials.
- Another advantage of the Bayesian method is the **introduction of prior** estimates at level III.
  - In complex models like the present one, priors can be useful for certain parameters difficult to estimate by a classical approach: for example prior information for cross-over correlation and between-study variances.

Extension of the approach to include non-comparative trials

- The Bayesian approach allows to include also information which comes from non-comparative trials (not further discussed today)

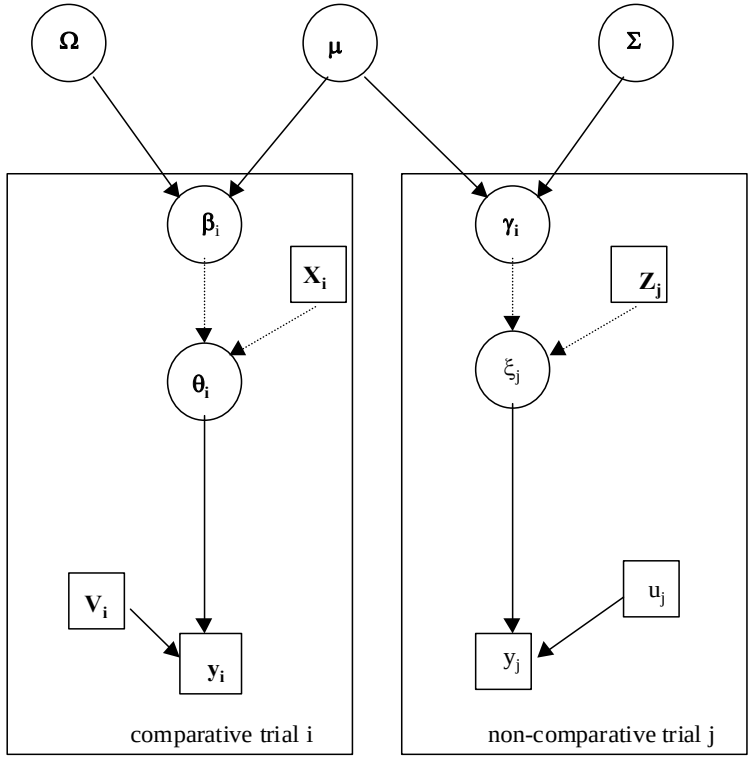


Figure 9.1. Directed acyclic graph for meta-analysis combining comparative and non-comparative trials with a Bayesian hierarchical model.

Fixed or Random effects?

Fixed or random

- In the choice between a fixed effects GEE meta-analysis or a random effects approach with RIGLS/Bayes, the same reflection as for simpler meta-analytic models should apply (see for example Borenstein et al 2010)
  - when there is a series of trials assessing a very similar clinical question, a fixed effects approach with a GEE regression could be proposed, using covariates to adjust for well identified sources of heterogeneity.
  - When the heterogeneity of the study designs goes beyond the well identified sources and when there is a need to generalise results, one should opt for random effects models.
- **Hierarchical Bayesian models** are certainly the most flexible of these models and allow to introduce easily several levels and random parameters which can be the most appropriate for the complexity of the combination of these different trial designs.

Limitations of the approach

- Limitations inherent to regression meta-analysis should be considered.
  - **aggregation bias** in meta-analyses using regression models.
  - Regressing group average outcomes on trial characteristics could lead to biases compared to the relationships observed at the individual level.
- However, in cross-over results reported in the literature, **details on the results by sequence are often missing** and it can be difficult to extract the appropriate contrasts and variance estimates necessary to feed the models and the information to compute covariates (Elbourne et al., 2002).
- Unless there is some direct access to the original trial reports, this **absence of information can be a severe limitation** for adjusting for these covariates and even **to include certain cross-over trials** in the pooled estimates.

In summary

- Marginal estimates of treatment effect can be combined from different trial designs
- Caution with the carry-over bias coming from cross-over trials
- Regression approaches with covariates explaining part of the heterogeneity are useful
- Random effects models are probably necessary- they may allow also to include information from non-comparative trials
- Access to the original trial data is key

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