

Planning and Analysis of Cross-over Trials in Infertility

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Acknowledgements

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Stephen

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- ISCB
 - This is my 24th ISCB and the 23rd at which I have presented

A Motivating Example

- Gregoriou et al 1996
 - Male infertility
- Compared intrauterine insemination (IUI) or timed intercourse (TI) in gonadotrophin stimulated cycles in couples with poor sperm quality
- 62 couples divided at random into two equal groups either IUI or TI for three cycles
- If failed to achieve pregnancy, switched to the other treatment

Two Views

CON

- The effect of treatment is not reversible
- There will be missing data
- This indication is inherently unsuitable for cross-over trials

PRO

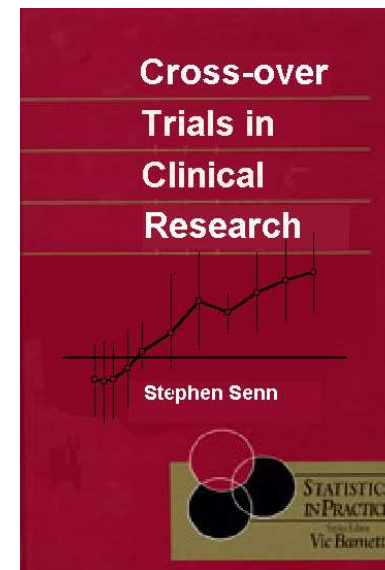
- What we have is a parallel group trial with some extra data
- How can more data be worse than fewer?
- There must be a way of analysing this

The viewpoint of an ‘authority’

‘Cross-over trials are most suited to investigating treatments for ongoing or chronic diseases: for such conditions where there is no question of curing the underlying problem which has caused the illness but a hope of moderating its effects through treatment.’

Who is this ‘authority’?

Stephen Senn



Data from Gregoriou et al

Sequence	Period 1	Period 2	Number of couples
TI/IUI	0	0	20
	0	1	7
	1	?	4
			31
IUI/TI	0	0	22
	0	1	1
	1	?	8
			31

Data from Gregoriou et al

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	1		8
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A Simple Analysis

- Treat the marginal table using the first period data and conditional table using the second period data as two strata
- Because the second table is a conditional table it can be treated as if independent of the first
- Apply the Mantel-Haenszel procedure using period as a stratifying factor

Analysis

Alternative tabulation of data

	Pregnancy Treatment	NO	YES
Period1	IUI	23	8
	TI	27	4
Period2	IUI	20	7
	TI	22	1

Mantel-Haenszel test

Test statistic: 4.198 on 1 d.f. (with continuity)

Probability: 0.040

Common odds ratio: 0.2870

95% confidence interval for common odds ratio (0.09550, 0.8625)

Note: Continuity corrected

log-odds ratio	RBG Standard error
1.248	0.5614

Different points of view?

- Some people can't conceive of any use for cross-over trials in infertility
- Others find them pregnant with possibilities
- And some think they can deliver if carefully used

A Random Effects Model

(Ezzet and Whitehead, 1992)

sequence i, subject j, period k

NB j nested within i

$$P(Y_{ijk} = y_{ijk}) = \theta_{ijk}^{y_{ijk}} (1 - \theta_{ijk})^{1 - y_{ijk}}, y_{ijk} = 0, 1.$$

$$\eta_{ijk} = \log \left[\frac{\theta_{ijk}}{1 - \theta_{ijk}} \right]$$

$$\eta_{ijk} = \mu + \phi_{ik} + \pi_j + \tau_{[i,j]}$$

$$\phi \sim N(0, \sigma^2)$$

This model has been *analysed* using maximum likelihood implemented in SAS and R. However, it has also been used to *simulate* results to be analysed using the MH approach and, indeed, other approaches considered..

Analysis of Gregoriou Example

	μ	τ	π
SAS®	-2.47 (0.95)	1.33 (0.64)	-0.18 (0.63)
R®	-2.53 (0.58)	1.34 (0.66)	-0.15 (0.58)
WinBugs®	-2.2 (0.54)	1.32 (0.59)	-0.31 (0.53)
GenStat®	-2.15 (0.51)	1.22 (0.56)	-0.25 (0.52)
MH		1.25 (0.56)	

Simulation: Null Case MH Analysis

Simulation of null case

$n=100$

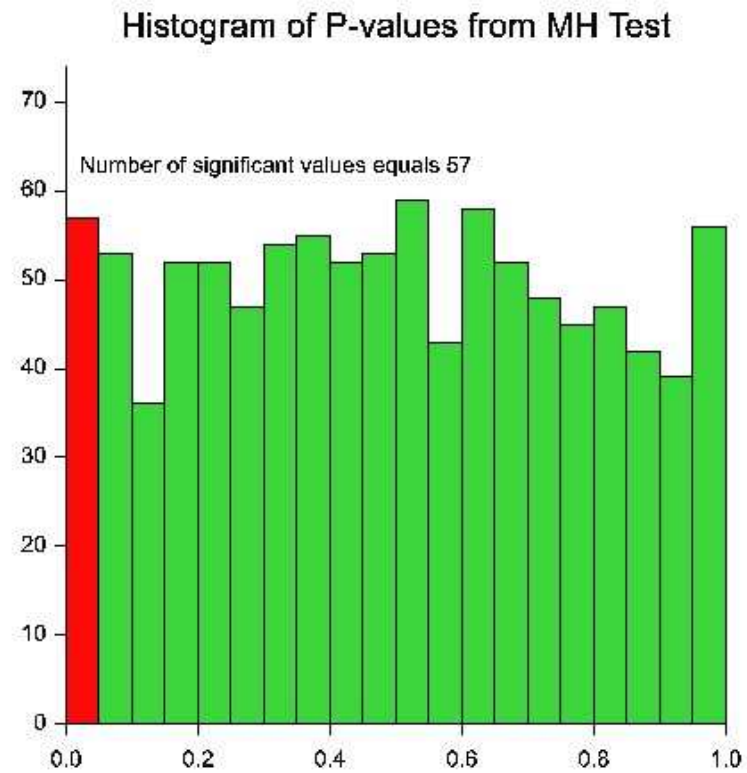
$\mu=0$

$\pi=0.1$

$\sigma=1$

$\tau=0$

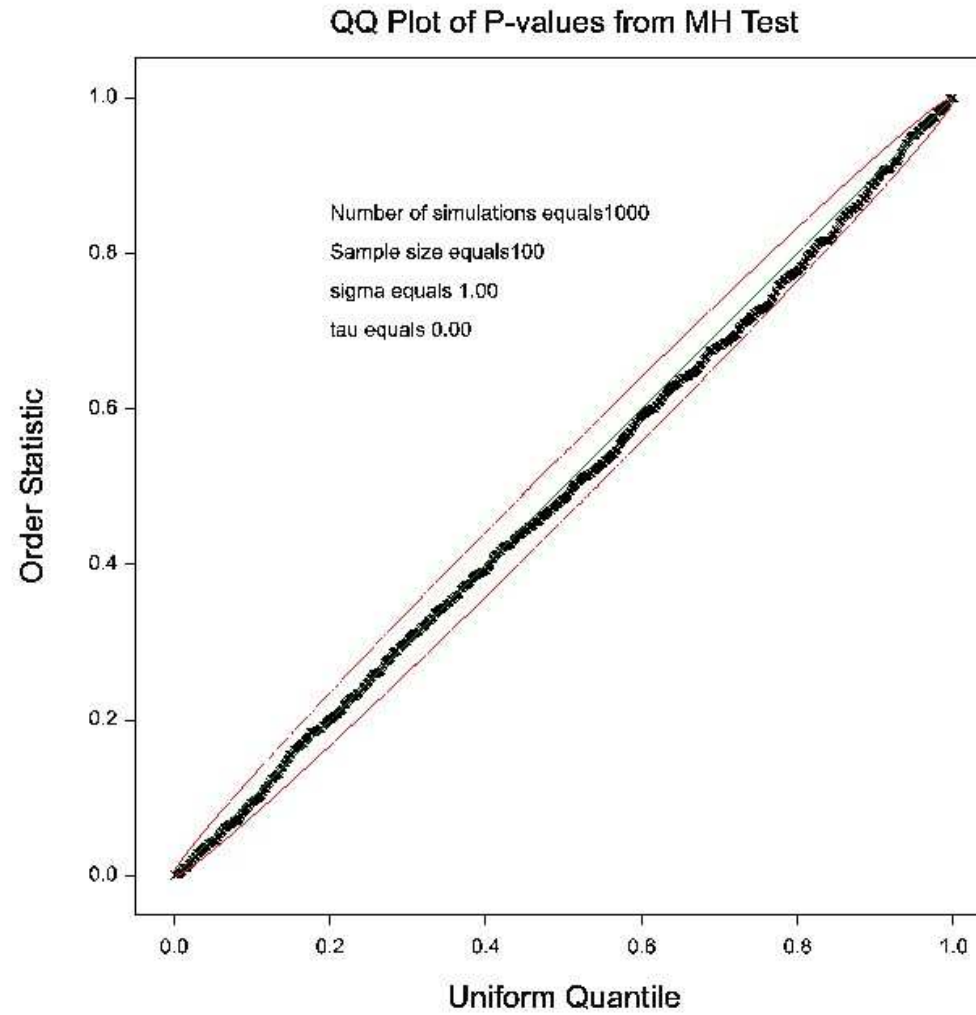
1000 simulations



sigma equals 1.00
tau equals 0.00

Number of simulations equals 1000
Sample size equals 100

Simulation: Null Case MH Analysis



Simulation: Alternative Case MH Analysis

Simulation of alternative case

$n=100$

$\mu=0$

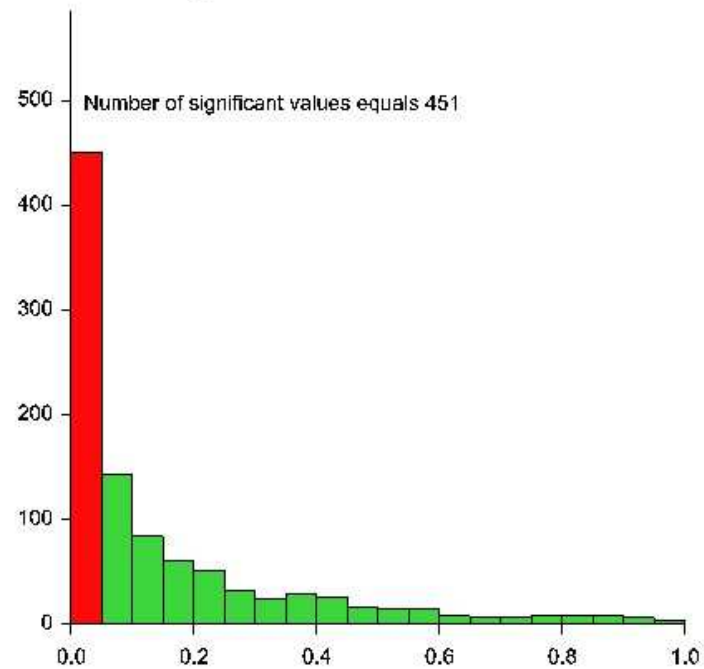
$\pi=0.1$

$\sigma=1$

$\tau=0.5$

1000 simulations

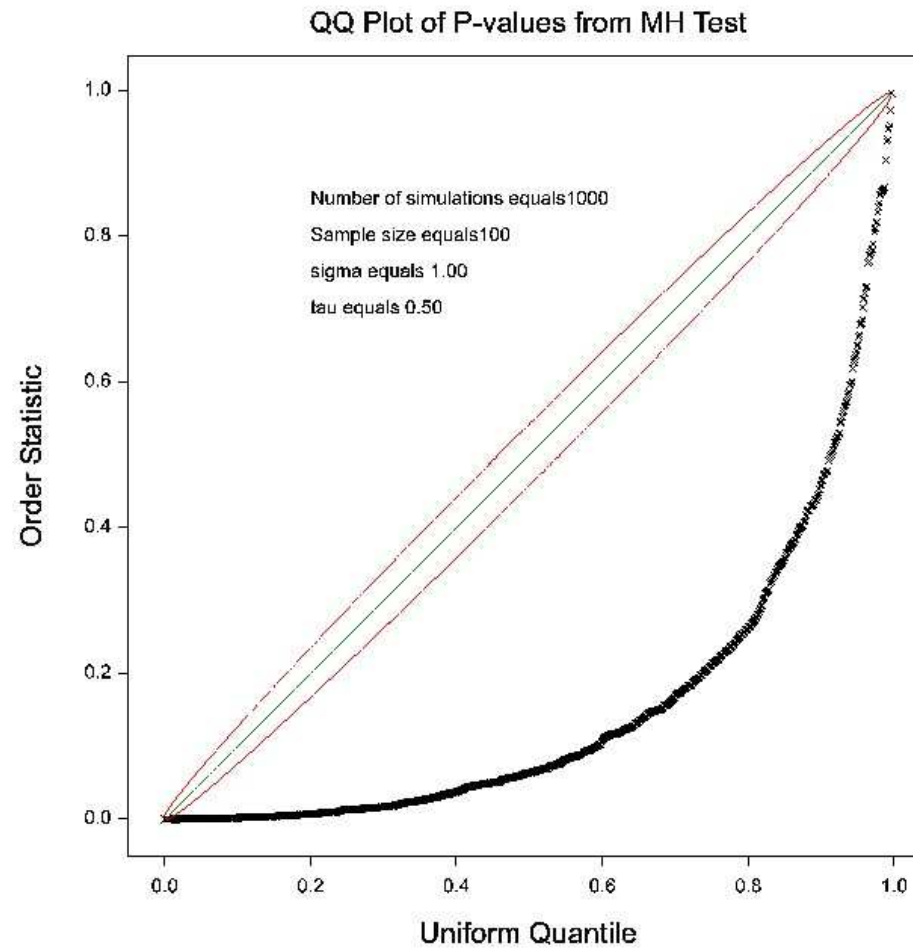
Histogram of P-values from MH Test



sigma equals 1.00
tau equals 0.50

Number of simulations equals 1000
Sample size equals 100

Simulation: Alternative Case MH Analysis



'Bias' in MH approach

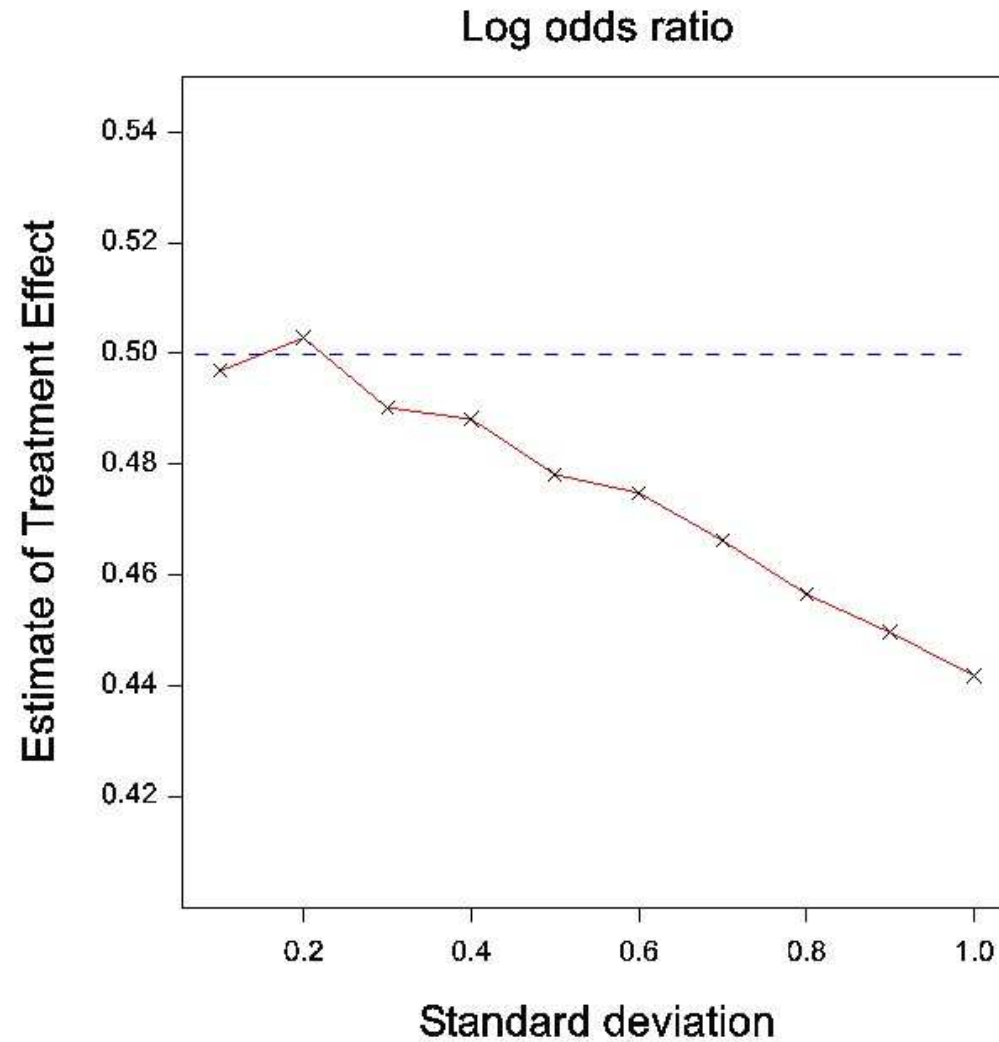
10000 simulations per setting

$n = 100$ as before

Standard deviation σ allowed to vary from 0.1 to 1

$\tau = 0.5$

Estimated log-odds ratio compared to conditional value



Two period crossover and Infertility crossover

- We simulated a two-period cross over design (2000 samples of size 300) using $\mu = -0.476$, $\tau = 0.856$, $\sigma = 0.351$.
- The simulation was done with the help of MathCad®.
- We remove the second outcomes for those women who conceived in the first period to get the realistic infertility trial.

Results

Method	μ	tau	Φ
Two-period	-0.482 (0.137)	0.87 (0.209)	0.342 (0.191)
Infertility trial	-0.479 (0.244)	0.881 (0.254)	0.302 (0.465)

Crossover and parallel

- We remove the second outcome from each woman to get the parallel trial
- Estimates obtained from parallel trial are marginal estimates.
- We compute the marginalized estimates from the crossover trial(s) and compare them with the marginal estimates from the parallel trial

Results

Method	Marginalized Mu	Marginalized Tau
Two-period crossover	-0.352 (0.097)	0.624 (0.149)
Infertility crossover	-0.353 (0.122)	0.627 (0.179)
Parallel trial	-0.354 (0.123)	0.63 (0.241)

Conclusion

- Think positive
 - Parallel group trials with added information
 - Not cross-over trials with missing information
 - The glass is half full not half empty
- Mixed non-linear models approach much more feasible nowadays
- But some puzzling discrepancies remain
- MH analysis provides simple back-up

Finally

Remember that cross-over trials refresh the parts of medical investigation other trials cannot reach