A career on the front-line: academic or support staff?

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“Building successful collaborations”

- “Front-line”?
- Career
  - Explain perspective
  - Lessons learned and role in collaborations
- Answer question of the title

Studentship

- Applied final year Medical Statistics option
  - Inspirational guest lecture
- Leicester MSc with excellent cohort

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What is meant by intention to treat analysis? Survey of published randomised controlled trials

Sally Hollis, Fiona Campbell

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BMJ 1999;319:670–4

Abstract

Objectives To assess the methodological quality of intention to treat analysis as reported in randomised controlled trials in four large medical journals.
Design Survey of all reports of randomised controlled trials published in 1997 in the *BMJ, Lancet, JAMA,* and *New England Journal of Medicine.*
Main outcome measures Methods of dealing with deviations from random allocation and missing data.
Results 119 (48%) of the reports mentioned intention to treat analysis. Of these, 12 excluded any patients who did not start the allocated intervention and three did not analyse all randomised subjects as allocated. Five reports explicitly stated that there were no deviations from random allocation. The remaining 99 reports seemed to analyse according to random allocation, but only 34 of these explicitly stated this. 89 (75%) trials had some missing data on the primary outcome variable. The methods used to deal with this were generally inadequate, potentially leading to a biased treatment effect. 29 (24%) trials had more than 10% of responses missing for the primary outcome, the methods of handling the missing responses were similar in this subset.
Conclusions The intention to treat approach is often inadequately described and inadequately applied. Authors should explicitly describe the handling of deviations from randomised allocation and missing responses and discuss the potential effect of any missing response. Readers should critically assess the validity of reported intention to treat analyses.

Introduction

"Intention to treat" is a strategy for the analysis of randomised controlled trials that compares patients in the groups to which they were originally randomly assigned. This is generally interpreted as including all patients, regardless of whether they actually satisfied the entry criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol. However there is a debate about the validity of excluding specific cases within each of these categories from an intention to treat analysis.[1] Clinical effectiveness may be overestimated if an intention to treat analysis is not done.[2]

The intention to treat approach has two main purposes. Firstly, the approach maintains treatment groups that are similar apart from random variation. This is the reason for randomisation, and the feature may be lost if analysis is not performed on the groups produced by the randomisation process. For example, in a trial comparing medical and surgical treatment for stable angina pectoris, some patients allocated to surgical intervention died before being operated on.[3] If these deaths are not attributed to surgical intervention using an intention to treat analysis, surgery seems to have a falsely low mortality (table 1). Secondly, intention to treat analysis allows for non-compliance

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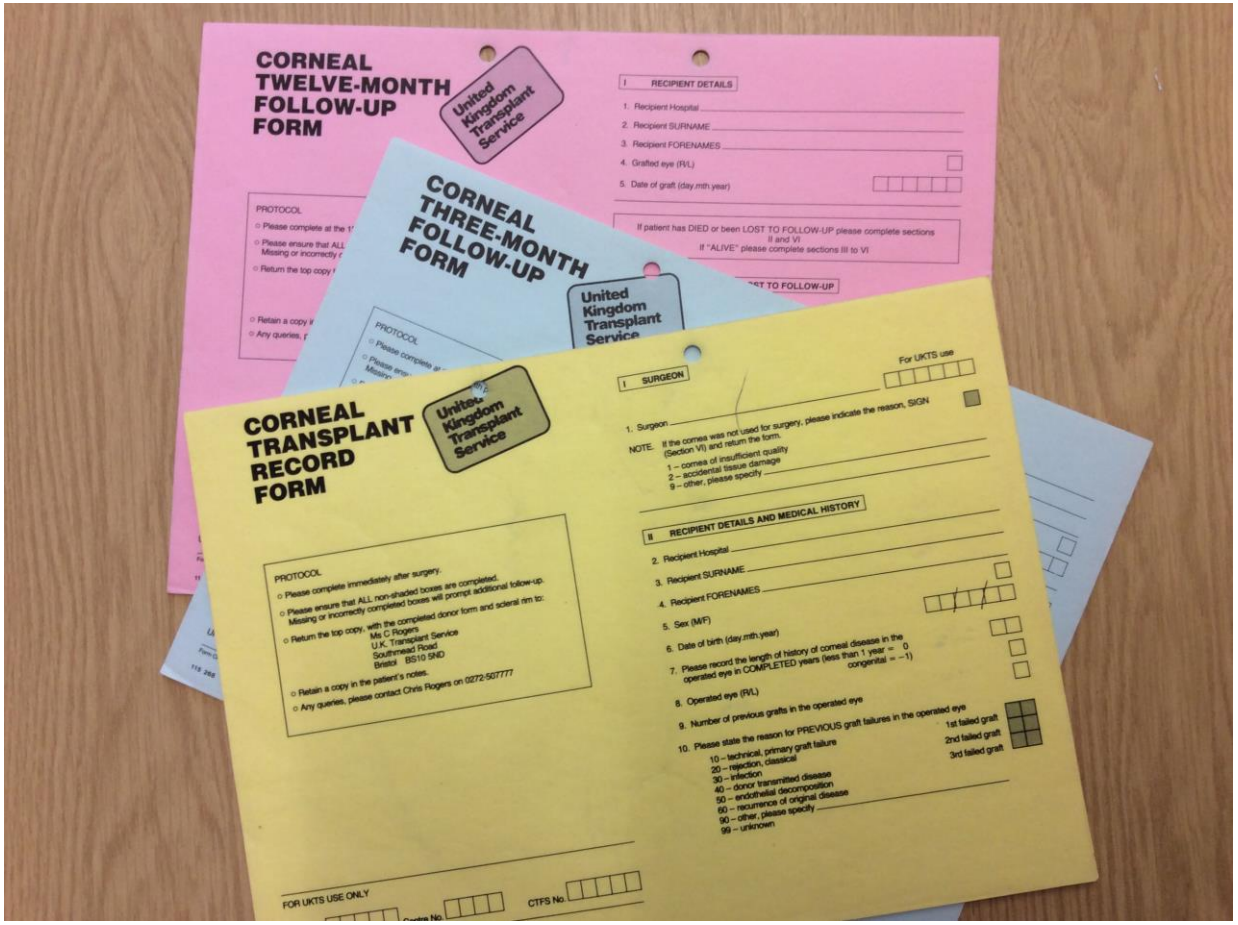
MSc Dissertation

- IARC, Lyons (WHO)
- Case-control study with 450,000 cases
- Age-period-cohort plus
  - Age, Year of Death, Year of birth
  - Age on arrival, Year of arrival
- Lesson 1: Don’t be blinded by science!

UK Transplant Service



Ready-made Collaboration

Typical ‘contract research’ position

- DoH-funded in NHS setting

- Pre-NIHR
  - NHS limit on % budget spent on research
  - Researchers transferred to University of Bristol

Many lessons!

- Lesson 2: Collaboration requires good will
  - Make it as easy as possible
  - PPI analogy for remote staff

- Lesson 3: Be a statistician
  - RSS & ISCB membership
  - Medical Section attendance

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Lesson 4: Understanding the data

Stratum	No.	Relative Risk*	P Value†
Indication for Graft			
No dystrophy	544	1.00	
Keratoconus	360	0.07 (0.03, 0.16)	
Corneal dystrophy	57	0.23 (0.07, 0.73)	P < 0.0001
First graft (ipsilateral)	834	1.00	
Second graft	99	3.80 (2.51, 5.76)	P < 0.0001
Third/subsequent graft	28	5.08 (2.69, 9.58)	
Inflammation, Vascularization, and IOP			
Never inflamed	521	1.00	
Inflamed in past	222	4.40 (2.53, 7.67)	
Inflamed at graft	37	9.60 (5.73, 16.09)	P < 0.0001
Inflamed in past, at graft	180	9.64 (4.50, 20.66)	
Unknown	1		
Avascular at graft	680	1.00	
Vascularized	281	2.74 (1.91, 3.95)	P < 0.0001
IOP never high	796	1.00	
IOP high in past	116	2.81 (1.85, 4.28)	P < 0.0001
IOP high at graft	28	1.95 (0.79, 4.83)	
Unknown	21		
Lens Status			
Phakic	529	1.00	
Aphakic	120	4.93 (3.00, 8.10)	P < 0.0001
Pseudophakic	295	2.99 (1.93, 4.62)	
Unknown	17		
No IOL	666	1.00	
Posterior chamber IOL	158	0.98 (0.57, 1.69)	
Anterior chamber IOL	108	2.50 (1.55, 4.02)	P < 0.0001
Iris-clip IOL	29	5.24 (2.88, 9.53)	
Other Factors			

Lesson 5: Disciplined thinking

- Appropriate interpretation of post-hoc analyses
- Surprising result contrary to study aim
  - Closer HLA-DR matching detrimental
- Biological plausibility: ‘docking hypothesis’

Lesson 6: Precise language

- No apology for pedantry
- E.G. no evidence of effect
- “There was no difference between men and women in our study”

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Academic expertise?

- Survival analysis
  - Time to first rejection, time to graft failure
- Statistical computing in infancy (BMDP)
  - Methods not familiar to clinicians
- Application and exposition
  - No methodological development

Leeds: Institute of Epidemiology & HSR

- Leeds General Infirmary funding for new post
  - Grateful to Richard Lilford's negotiating skills
- What's in a name?
  - Focus on clinical research in Obstetrics, Midwifery, Gynaecology
- Academic?
  - 'Academic related, other related' post

Professional Isolation

- "Make yourself useful"
  - Great for freedom, no mentoring
- Other statisticians sparsely distributed
  - Public Health, LRF Epidemiology, Cancer Registry and Trials Unit
- "Foster good relations"
  - Seminar series, RSS, Rounders matches!

Diverse collaborations

- Peer collaboration
- Small scale
- Large scale
- Massive

Peer Collaboration: Research Ethics

- COREC working party
- Richard Lilford interested in ethics
  - Encouraged REC membership
- ISCB presentation, SiM paper
- cf Burwalls, NIHR Statistics specialty groups

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Academic contribution?

- Experiential rather than novel

Table I. Principal queries (one per study) arising over an 8 month period

Therapeutic intervention studies ($n = 79$)	Other studies ($n = 76$)
8 Blinding	4 Ill-defined
6 Randomization	3 Groups
5 Placebo	2 Clarity
3 Groups	2 Future treatment
2 Clarity; Cross-over	1 Sample size
1 Benefit from participation; information; sample size	

Small scale: known locally

- Most CTFS papers after move to Leeds
- 'Found' by Leeds ophthalmologist
  - Geriatrician concerned by beta-blocker use
  - No major funding
  - RCTs of licensed medications
- Academic role?
  - Standard methods, pinned down questions

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Impact

THE LANCET

Avoiding unsuspected respiratory side-effects of topical timolol with cardioselective or sympathomimetic agents

Paul Diggory, Andrew Cassels-Brown, Andy Vail, Linda Mary Abbey, Jeffry Stewart Hillman

Summary

Topical timolol given for the treatment or chronic simple glaucoma may cause unrecognised bronchospasm among elderly people.

Introduction

Chronic simple glaucoma affects more than 1 in 20 elderly people.[1] Topical timolol, a non-selective beta-antagonist, is the most frequently prescribed treatment,

British Journal of Ophthalmology 1998;82:146–149

Randomised, controlled trial of spirometric changes in elderly people receiving timolol or betaxolol as initial treatment for glaucoma

P Diggory, A Cassels-Brown, A Vail, J S Hillman

Large scale

Jim Thornton: obstetrician with fundamental question

When should he deliver the pre-term infant that is failing to thrive?

Gestational Age (weeks)

EDF

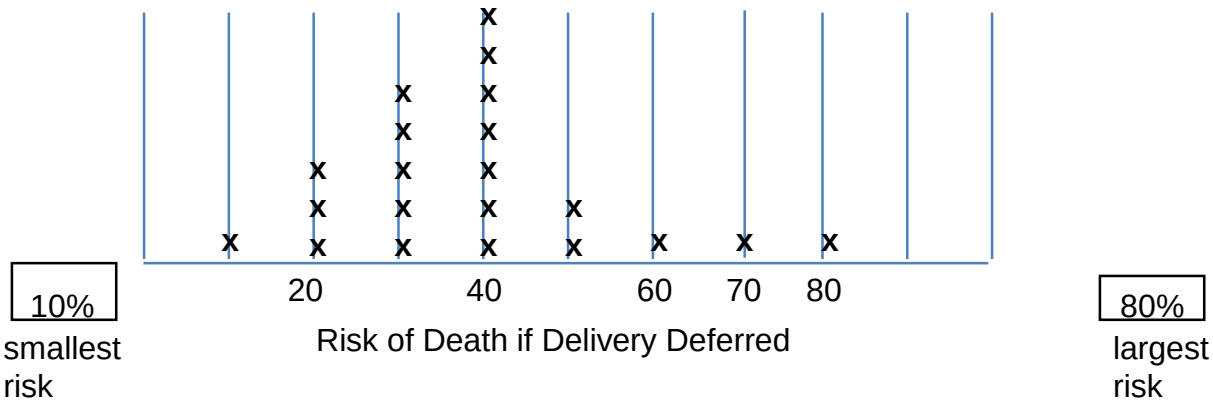
	24-25	26-27	28-30	31-34	35-36
Reversed	?	?	I	I	I
Absent	D	?	?	I	I
Low	D	D	?	?	I
Moderate	D	D	D	D	?

Elicitation Exercise

Example : Collaborator 6

Clinical Scenario: *Absent EDF at 28-29 weeks*

Risk of Death if Delivery: Immediate 20%
Deferred 40%



Extreme views

- DGH Consultant
  - Death on immediate: 70%
  - Odds Ratio: 4.3 (2.3 to 9.3)

- Fetal Medicine Senior Registrar
  - Death on immediate: 20%
  - Odds Ratio: 0.2 (0.05 to 0.3)

Recruitment

- Surgical reticence (pre Jenny Donovan work)
- All happy in principle but…
  - No consensus on eligibility criteria
  - Committed decision makers
- Needed radical solution

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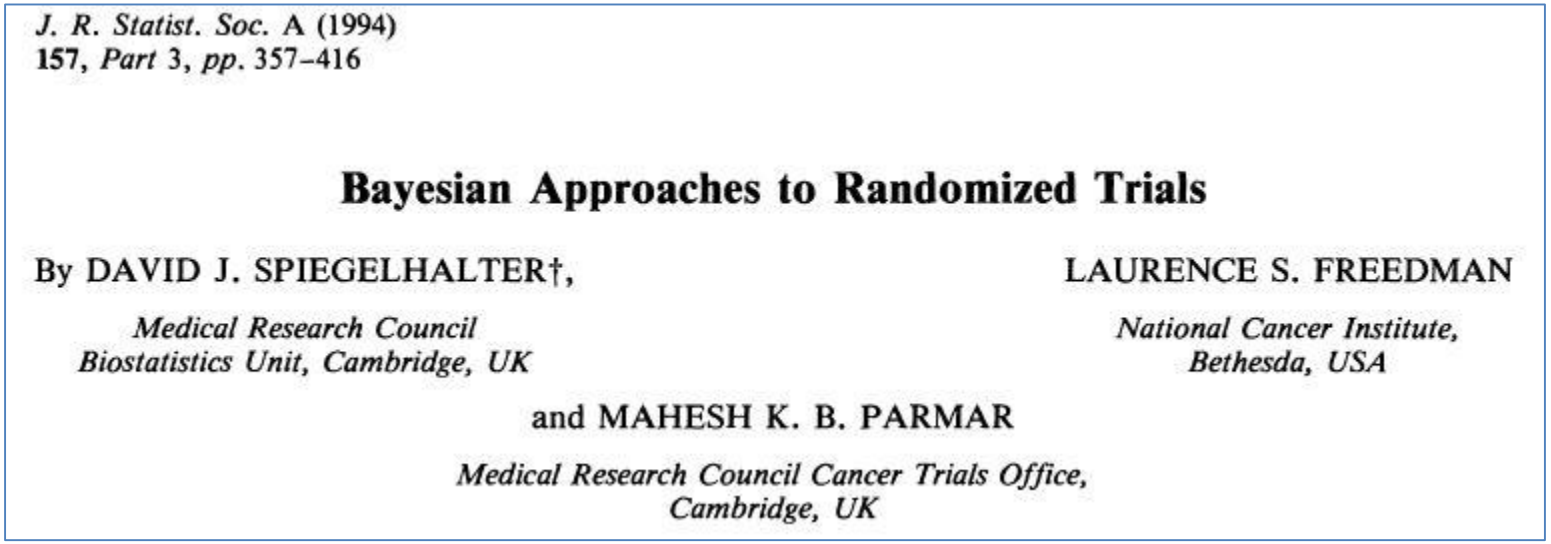
Time for Bayes?

- Culture shift in applied biostatistics
  - Driven by possibility and pragmatism?
- Subjectivity objection removed
- Novelty appealed to potential recruiters
  - Would it appeal to funders?

Needed convincing team



J. R. Statist. Soc. A (1994)
157, *Part* 3, *pp.* 357–416

Bayesian Approaches to Randomized Trials

By DAVID J. SPIEGELHALTER†,

Medical Research Council
Biostatistics Unit, Cambridge, UK

LAURENCE S. FREEDMAN

National Cancer Institute,
Bethesda, USA

and MAHESH K. B. PARMAR

Medical Research Council Cancer Trials Office,
Cambridge, UK

- Lesson 7: Don’t be afraid to ask

Successful Collaboration

STATISTICS IN MEDICINE
Statist. Med. 2001; **20**:3777–3787 (DOI: 10.1002/sim.1171)

Prospective application of Bayesian monitoring and analysis in an 'open' randomized clinical trial‡

A. Vail[1,*,†], J. Hornbuckle[2], D. J. Spiegelhalter[3] and J. G. Thornton[2]

[1] *Biostatistics Group, University of Manchester, Manchester, U.K.*
[2] *Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds, Leeds, U.K.*
[3] *MRC Biostatistics Unit, Cambridge, U.K.*

Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial

The GRIT study group*

Lancet 2004; 364: 513–20
See Comment page 483
*Members listed at end of report

Correspondence to:
Prof J G Thornton, Division of Obstetrics and Gynaecology, City Hospital, Nottingham NG5 1PB, UK

Summary

Background Although delivery is widely used for preterm babies failing to thrive in utero, the effect of altering delivery timing has never been assessed in a randomised controlled trial. We aimed to compare the effect of delivering early with delaying birth for as long as possible.

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Academic contribution?

- Novel application
- Minor extension of method
- Far from academic expertise in Bayes

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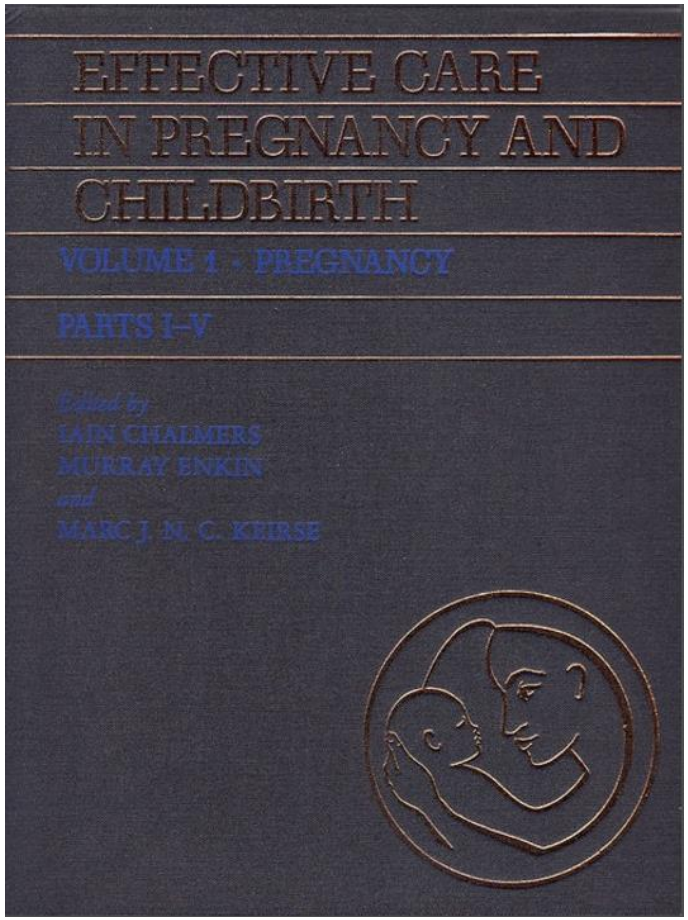
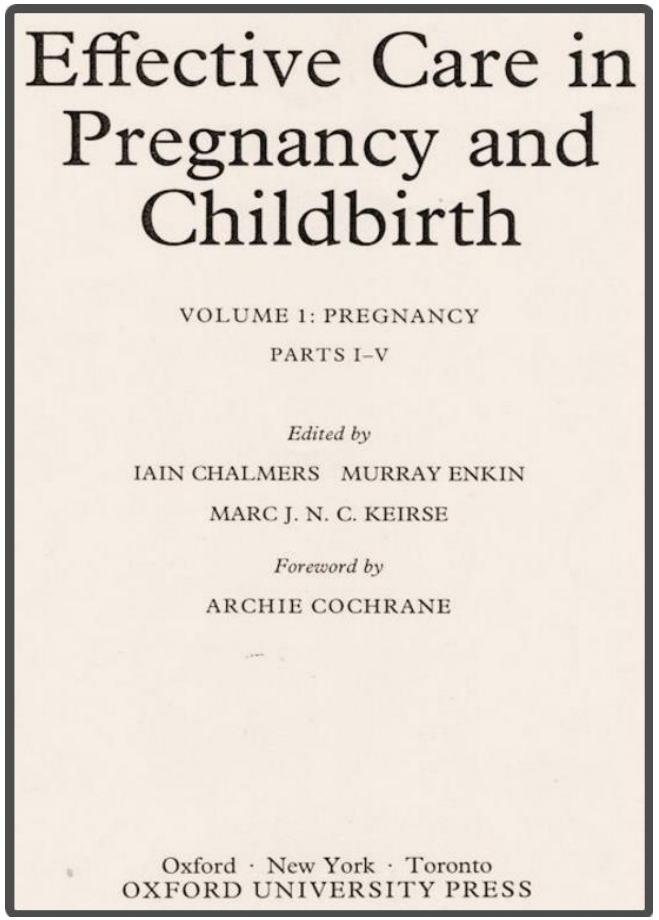
The University of Manchester

Massive: Cochrane





Collaboration

- Richard Lilford subfertility reviews
- Iain Chalmers regular visitor
  - Force of personality
  - Force of argument
  - Dogged persistence
- Academic role?
  - Programmed methods pre RevMan software

Hope (Salford Royal) Hospital

- Graham Dunn appointed at Manchester
  - Remembered Lesson 7: Seminar invitation

- Post at Hope R&D Support Unit
  - Identical remit but hospital based
  - Jointly funded by Children's Hospitals
  - Agreed transfer to Univ post

Continuing Collaborations

- More GRIT
  - Long-term paediatric follow-up
  - IPD meta-analyses

- More Cochrane

Cross-over with terminal outcome (1)

FERTILITY AND STERILITY®
VOL. 74, NO. 2, AUGUST 2000

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

REPRODUCTIVE ENDOCRINOLOGY

The alternating-sequence design (or multiple-period crossover) trial for evaluating treatment efficacy in infertility

Conclusion(s): When multiple cycles of treatment are undertaken to evaluate the efficacy of infertility therapy, the alternating-sequence design with restriction of the analysis to only the odd-numbered treatment cycles provides an unbiased estimation of the treatment effect. (Fertil Steril® 2000;74:319–24. ©2000 by American Society for Reproductive Medicine.)

Cross-over with terminal outcome (2)

- From ISCB 2003

CONTRIBUTED ORAL PRESENTATIONS O:18

THE ANALYSIS OF CROSSOVER TRIALS FOR INFERTILITY TREATMENT

"Curiously, when in fact the data are generated through a constant Odds ratio, analysis will only give correct results in even-numbered cycles"

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Lesson 8

Simulation studies find what they simulate

- Or is this Lesson 1?
  - Need to remember what cross-over trials are

- Academic role?
  - Mainly exposition
  - Supervision of statistical staff

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New Collaborations

- Active research in neuroscience, rheumatology, dermatology
- Methods for experimental design, healthy and disease cohorts, measurement, prognosis, diagnosis, intervention,…

Too broad?

- Time for understanding of clinical context?
  - Depend more on close collaboration
  - Experience to ask the right questions
  - Recommend visit to see data collection

- Recurring ‘annual review’ feedback to focus
  - Competing demand of funding

NIHR Benefits

- Clinicians doing clinical research!
- Statisticians highly valued
- Increased opportunities to engage
  - Funding panels
  - RCT oversight committees
  - Research Design Service
  - Accredited CTUs

RCT regulation

- Previously passed MHRA inspection
  - Funding and sponsorship challenging
- Massive increase in trial quality at price
  - Horrors occurred
  - Glaucoma collaboration still possible?
- Zermansky study
  - 4 practices, 1200 patients, 1-yr follow-up
  - HTA-funded for £140k (£220k today)

Back to the point!

Academic or support?

- Not pursued specific method or clinical area
  - Survival, Bayes, Trials, Meta-analysis, Observational studies, Experimental design,…
  - Corneas, Obstetrics, Infertility, Glaucoma, Pharmacy, Stroke,…
- Dabbler? Jack of all trades?

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What makes a (good) statistician?

- RSS avoids definition
- Bland: “Statistics is a skill as well as a science…The true statistician is much more interested in the process of answering the question than the answer itself…entire purpose is to solve problems in other disciplines”
- Senn: “not simple common sense”

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NIHR Statistics Meeting
HMS Belfast 2016

- Deborah Ashby – statistician or non-statistician?
- Expertise not in specific cutting edge methods
  - Rarely analyse data
- Should value our statistical thinking
  - Logical, independent

Examples from/for clinical meetings

- Probability that God exists?
- Estimate proportion of cats
- Interview exercises for consultancy roles

Multi-disciplinary collaboration

- Need to avoid
  - perception as department's 'pet statistician'
  - professional isolation
- Original thinking is required
- Role in education of colleagues

Academic or support staff?

Our role is academic

At its best, our academic expertise does provide support for other disciplines, for research, and for current and future patients