NIHR, BIG data and how to avoid statistical errors

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OAA
Torquay
2015
“Compare like with like.....”
We've run out of lab rats, Henderson... Put this on and come with us.
The Research Pathway

**INVENTION**
- Creation
  - new things
  - new ideas
  - new techniques
  - new approaches

**EVALUATION**
- Assessment
  - new things
  - new ideas
  - new techniques
  - new approaches

**ADOPTION**
- Uptake
  - new things
  - new ideas
  - new techniques
  - new approaches

**DIFFUSION**
- Spread
  - new things
  - new ideas
  - new techniques
  - new approaches

**Basic Research**
- MRC

**Applied Research**
- NIHR

**Commissioning**
- Commissioners

**Patient Care**
- Providers of NHS Services

**Better Quality**
**Better Value**
To improve the health and wealth of the nation through research

- Established in 2006 as part of “Best Research for Best Health”; a Government Strategy
- Budget approximately 1% of NHS spend (£1billion)
- Goals:
  - Transform research in the NHS
  - Increase the volume of applied health research for the benefit of patients and the public
  - Develop and support the people who conduct and contribute to applied health research
  - Support industry and growth
Number of Open Studies by main topic (UK-wide)
Anaesthesia: Plenty of Scope for doing more!

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Number of Consultants</th>
<th>Number of studies</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatology</td>
<td>31</td>
<td>36</td>
<td>0.9</td>
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<tr>
<td>Critical care</td>
<td>73</td>
<td>45</td>
<td>1.6</td>
</tr>
<tr>
<td>Genetics</td>
<td>197</td>
<td>81</td>
<td>2.4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>856</td>
<td>229</td>
<td>3.7</td>
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<tr>
<td>Respiratory</td>
<td>859</td>
<td>160</td>
<td>5.4</td>
</tr>
<tr>
<td>Nervous Sys D</td>
<td>633</td>
<td>112</td>
<td>5.7</td>
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<tr>
<td>Renal</td>
<td>502</td>
<td>66</td>
<td>7.6</td>
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<tr>
<td>Dermatology</td>
<td>607</td>
<td>55</td>
<td>11.0</td>
</tr>
<tr>
<td>GI</td>
<td>995</td>
<td>81</td>
<td>12.3</td>
</tr>
<tr>
<td>Age and Ageing</td>
<td>1205</td>
<td>35</td>
<td>34.4</td>
</tr>
<tr>
<td>Surgery</td>
<td>3766</td>
<td>60</td>
<td>62.8</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>6233</td>
<td>27</td>
<td>230.9</td>
</tr>
</tbody>
</table>

Ratio of studies to consultants
RESPITE
A Randomised Controlled Trial of Remifentanil intravenous Patient Controlled analgesia (PCA) versus intramuscular pethidine for pain relief in labour

ISRCTN29654603
EUDRACT # 2012-005257-22
Effect site concentration

![Graph showing the effect site concentration for different opioids: Remifentanil, Sufentanil, Pethidine, and Alfentanil. The graph plots percent peak Ce against time since bolus in minutes.](image-url)
Remifentanil vs. Pethidine

- Superior analgesia
- ↑Maternal satisfaction
- Sedation similar

- Fetal effects equivalent
  - Heart Rate
  - APGAR 5°
  - Acidosis
  - Neurobehavioral

The Health and Social Care Act (2012)

• Places a clear duty on the Secretary of State, the NHS Commissioning Board and Clinical Commissioning Groups to promote research on matters relevant to the health service, and the use in the health service of evidence obtained from research

• NHS Constitution: clinical research is “core business” for the NHS; patients have a right to participate in a clinical trial if they are suitable for it

• Rapid adoption of effective innovations to characterise NHS
NHS Constitution: article 3a includes a "pledge" to inform patients when they "may be eligible" to participate in a research study
Respite trial: PPI rep

"I wanted to take part. I read about it, tried to meet people who could help, and even put it in my birth plan. They just weren't interested. It was really upsetting."
Hierarchy of evidence based medicine

Individual experience
Collective experience
Case report
Case series
Cohort: observational
Cohort: case control
Randomised Controlled Trials
Meta-analysis of RCTs
Evidence

We don’t have to study everything

Parachute or snowboard, jumping out of a plane?
Evidence

• Doing the study doesn’t always mean we find the right answer: generalisability
Case reports


Novel treatment (new drug/intervention; established drug/procedure in new situation)

Successful pregnancy following mid-trimester evacuation through a transabdominal cervical cerclage

Manju Chandiramani, Lucy Chappell, Samara Radford, Andrew Shennan

Division of Reproduction and Endocrinology, Maternal and Fetal Research Unit, Department of Women’s Health, St Thomas’ Hospital, King’s College London, London, UK

Correspondence to  Dr Manju Chandiramani, manju.chandiramani@kcl.ac.uk

Summary
Preterm birth remains a major challenge in modern obstetrics and is increasing, even among low-risk primiparous women. Very few interventions have made a positive impact on outcome although cervical cerclage appears to benefit some women. Transabdominal cervical cerclage can be highly successful and should be considered in women with previous failed transvaginal cerclage, but requires operative abdominal delivery as it cannot be removed. The authors report the first case they are aware of, where a spontaneous abortion occurred with a transabdominal cerclage in situ and a mid-trimester dilation and evacuation was performed through the cerclage at 18 weeks gestation.
Statistical errors.... lies, damn lies and statistics

Type I Error

You're pregnant

Type II Error

You're not pregnant
Statistical Errors

- 0 Right answer wrong question
- 1 A difference exists that isn't real
- 2 No difference is found when one exists
- 3 Significant answer, wrong direction
- 4 Errors in assays, machines, labelling
- 5 Made up, fraudulent
Type 1 error (Plausibility)

- RCT
- Placebo controlled
- Predefined primary endpoint; pre-eclampsia
- Predefined analysis
- Significant difference: RRR 0.8 (CI 0.71 – 0.89), p <0.001
- Population:
  Odd numbers vs even numbers
Type 1 error (predefined endpoint)

Number of women with pre-eclampsia

Intention-to-treat
Completed study

Placebo
Vitamins C and E
Predefined primary endpoint

Effect of vitamins on PAI-1/PAI-2 ratio

Chappell et al 2002
Why is \( p < 0.05? \)

Alpha, or chance of False Positive?

Because we have 5 fingers
**Fetal Monitoring: Type 2 errors?**

Review: Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour
Comparison: 01 Continuous CTG versus intermittent auscultation (all)
Outcome: 26 Neonatal seizures

<table>
<thead>
<tr>
<th>Study</th>
<th>CTG n/N</th>
<th>Auscultation n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
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</thead>
<tbody>
<tr>
<td>01 Continuous CTG and FBS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copenhagen 1985</td>
<td>0/485</td>
<td>0/403</td>
<td></td>
<td>0.0</td>
<td>Not estimable</td>
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<tr>
<td>Denver 1970</td>
<td>0/230</td>
<td>1/110</td>
<td></td>
<td>3.9</td>
<td>0.17 [0.01, 4.11]</td>
</tr>
<tr>
<td>Dublin 1985</td>
<td>12/0530</td>
<td>27/0554</td>
<td></td>
<td>53.0</td>
<td>0.46 [0.23, 0.88]</td>
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<tr>
<td>Melbourne 1970</td>
<td>0/175</td>
<td>4/175</td>
<td></td>
<td>8.9</td>
<td>0.11 [0.01, 2.05]</td>
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<tr>
<td>Seattle 1987</td>
<td>7/122</td>
<td>7/124</td>
<td></td>
<td>13.7</td>
<td>1.02 [0.37, 2.81]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>7542</td>
<td>7402</td>
<td></td>
<td>70.4</td>
<td>0.40 [0.29, 0.84]</td>
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<tr>
<td>Total events: 19 (CTG), 30 (Auscultation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for heterogeneity chi-square=3.40 df=3 p=0.33 I² =13.4%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect z=2.81 p=0.000</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>02 Continuous CTG only</td>
<td></td>
<td></td>
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<tr>
<td>Athens 1903</td>
<td>0/740</td>
<td>2/682</td>
<td></td>
<td>5.1</td>
<td>0.18 [0.01, 3.80]</td>
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<td>Dallas 1988</td>
<td>1/7288</td>
<td>3/7330</td>
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<td>5.9</td>
<td>0.34 [0.03, 3.22]</td>
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<tr>
<td>Denver 1970</td>
<td>2/242</td>
<td>2/241</td>
<td></td>
<td>3.9</td>
<td>1.00 [0.14, 7.01]</td>
</tr>
<tr>
<td>Denver 1979</td>
<td>2/233</td>
<td>1/110</td>
<td></td>
<td>2.6</td>
<td>1.00 [0.09, 10.87]</td>
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<tr>
<td>Sheffield 1978</td>
<td>0/253</td>
<td>1/251</td>
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<td>3.0</td>
<td>0.33 [0.01, 8.08]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>8762</td>
<td>8620</td>
<td></td>
<td>20.6</td>
<td>0.51 [0.18, 1.44]</td>
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<tr>
<td>Total events: 5 (CTG), 9 (Auscultation)</td>
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<td></td>
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<tr>
<td>Test for heterogeneity chi-square=1.40 df=4 p=0.84 I² =0.0%</td>
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<tr>
<td>Test for overall effect z=1.28 p=0.2</td>
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<td></td>
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<tr>
<td>Total (95% CI)</td>
<td>10304</td>
<td>10082</td>
<td></td>
<td>100.0</td>
<td>0.50 [0.31, 0.80]</td>
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<tr>
<td>Total events: 24 (CTG), 48 (Auscultation)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for heterogeneity chi-square=4.88 df=8 p=0.77 I² =0.0%</td>
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<tr>
<td>Test for overall effect z=2.91 p=0.004</td>
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</tbody>
</table>
Randomised trials

• INFANT

  – Intelligent decision support in the interpretation of the intrapartum CTG in labour
    - 46,000 women
  – Eligibility – women who are judged to require continuous electronic fetal monitoring in labour
  – Outcome – NE, IP stillbirth
INFANT

Antenatal information supplied to all women

All labour ward admissions ≥35 weeks except gross fetal abnormality, arrhythmia, triplets or higher

Intermittent auscultation
Decision made to initiate continuous EFM
Continuous electronic fetal monitoring

Randomisation

Control Arm
CTG monitoring with no decision support

Intervention Arm
CTG monitoring with decision support
Infant: Primary outcome

• “Poor neonatal outcome”:
  • Deaths (excluding congenital anomalies):
    – Intrapartum stillbirth
    – Neonatal
  • Neonatal encephalopathy:
    – Severe/moderate
    – Mild
  • Other significant morbidity:
    – Other admissions to NICU within 48 hrs of birth for ≥ 48 hrs e.g. respiratory symptoms, seizures

• Developmental quotient at age 2 years
INFANT Sample size

Assuming:
Poor neonatal outcome rate:
  3 per1000 births
• 5% significance level
• 90% power
  – 50% reduction in poor neonatal outcome rate
e.g. to compare 3 versus 1.5 per 1000

Need: 46,000 births in total (22,279 per arm)
RCT (event rate also important)
Seat belt vs No seat belt

20,000,000 Car Journeys/day

10,000,000 Seat Belt
10,000,000 No Seat Belt
RCT:
Seat belt vs No seat belt

20,000,000 Car Journeys/day

Seat Belt: 2 deaths
No Seat Belt: 8 deaths
Conclusions?

• Seat belts do not save lives, and should be abandoned as they limit the comfort and mobility of the passenger.
Conclusion

• This study is underpowered to determine the effect of seat belts on saving lives.
Type 3 error

Proportion of mothers giving birth, by gestational age and randomised treatment: A[____] or B[---]
TOCOX—A randomised, double-blind, placebo-controlled trial of rofecoxib (a COX-2-specific prostaglandin inhibitor) for the prevention of preterm delivery in women at high risk

Katie M. Groom, Andrew H. Shennan, Bryony A. Jones,
Paul Seed, Phillip R. Bennett
A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study

BJOG. 2006 Jan;113(1):65-74

Andrew Shennan, Sarah Crawshaw, Annette Briley, Jenny Hawken, Paul Seed, Griff Jones, Lucilla Poston

N=900 screened / 100 randomised
Studies involving metronidazole without erythromycin only

- Morales W et al., 1994
- McDonald H et al., 1997
- Carey J et al., 2000
- Klebanoff M et al., 2001
- Odendaal H et al., 2002
- Premet, 2004

Combined
Type 4 error

COMET trial
Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial

The Lancet, Volume 358, Issue 9275, Pages 19 - 23, 7 July 2001
The COMET study Group Shennan et al.

![Graph showing % SVD for Trad, CSE, and LDI with N=1054 (x2) and P=0.04]
Cochrane: feeding is safe?
Type 0?? Right answer, wrong question

A Randomised Controlled Trial to Evaluate
the Effect of Food intake during Labour
on Obstetric Outcome

SVD

N=2500
Maternal deaths due to anaesthesia

(1952-2008)

Number of deaths

Middle year of triennium

Other

Aspiration
Beware the hidden agenda!
Restricting oral intake in labour

“No benefit or harm, therefore do not restrict……”
• No studies looked specifically at women at increased risk of complications, hence there is no evidence to support restrictions in this group of women.
Should women drink/eat during labor?

We will never have the clinical trial evidence to ensure safety but in recent years we have seen....

- No increase in pulmonary aspiration
  - (4 deaths in 10,000,000 deliveries in UK)

In spite of....

- Considerable Increase in feeding practice
- Increase in C/S and therefore now GAs
Type 5 error.....
Malcolm Pearce

• Obstetrician suspended after research inquiry.

• Faked a report about transplantation of an ectopic pregnancy.
Upright versus recumbent position in the second stage of labour in women with combined spinal-epidural analgesia

M. Golara, MRCOG, F. Plaat, FRCA, A.H. Shennan, MD MRCOG


Length labour (minutes)

N=66
NIHR Health Technology Assessment Program
ISRCTN 35706297
Research model

- Multicentre RCT
- 41 Units
- N=3050
- 1 year pilot phase
- 2 years recruitment

£3.2M
Singleton, cephalic, term, nulliparae
Mobile epidural

Enter 2nd Stage

Upright
Lying Down

Power: 0.9
To detect a RR SVD
0.6

N=3237
Reporting 2015
Funding bodies

- Wellcome
- MRC
- NIHR
  - HTA
  - RfPB
  - Fellowships
- National Charities

“The harder it is, the less likely someone else is going to do it.”
Conclusion

• Research informs everything we do
• Research active clinicians have better outcomes
• We have an obligation to offer research to our patients, and many want it
• Publishing your experience disseminates your knowledge to many and forever
• Research is personally rewarding
• UK provides a globally unique opportunity to engage with health research
• Academics live longer
Geraldine O’Sullivan

Befriend an Obstetric Anaesthetist
Befriend a clinical academic
The Future….

Anaesthesia and perioperative care priority setting partnership