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Patient-reported outcomes as individual-level interrupted time series in observational studies

A workshop for chief investigators, trial managers, statisticians, patients and others with an interest in improving the quality of non-randomised healthcare evaluations

Friday 06 July 2018

Overview of the PROMiSe study

Richard Hooper

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Collaborators

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Edinburgh Clinical Trials Unit
Imperial Clinical Trials Unit
Clinical Effectiveness Group, QMUL

UNIVERSITY OF BIRMINGHAM

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www.qmul.ac.uk/pctu

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Funding

NIHR CTU Support Funding

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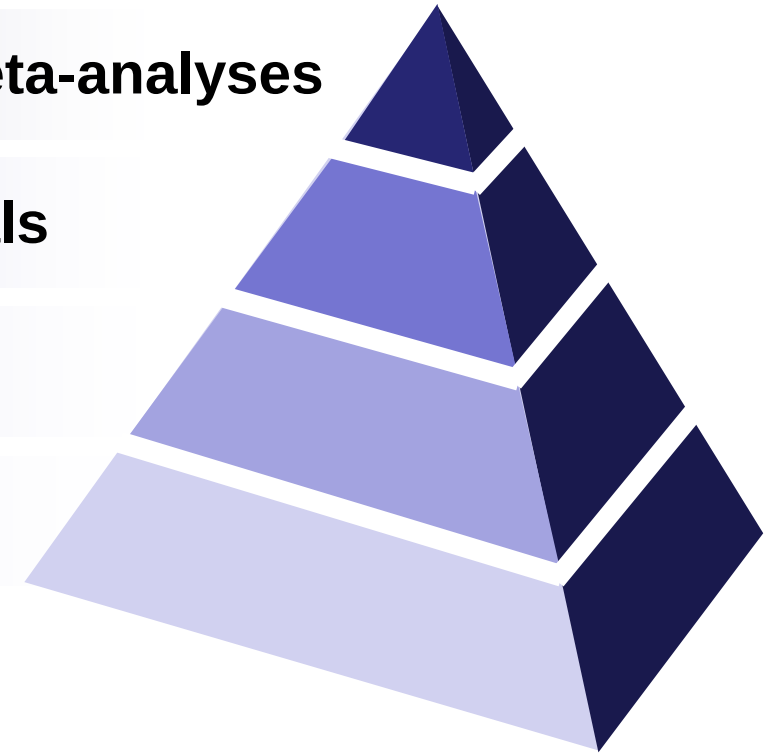
Pyramid of evidence in medical research

- Systematic reviews and meta-analyses
- Randomised controlled trials
- Observational studies
- Case reports



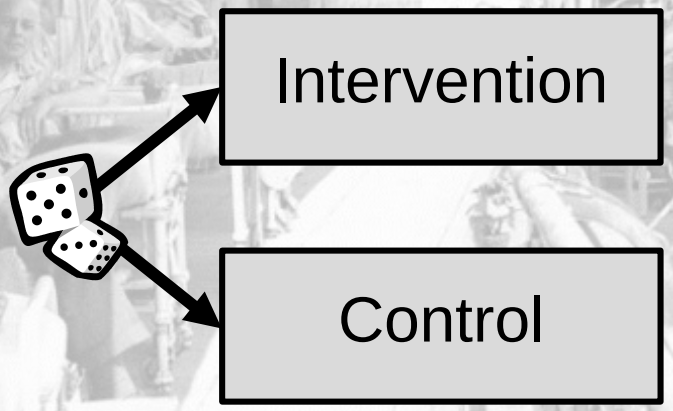
Randomised controlled trials – year zero:

the 1948 MRC streptomycin trial

Austin Bradford Hill

Randomised controlled trials – year zero:

the 1948 MRC streptomycin trial

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Why trials are like bicycles

Marginal gains

https://www.trialforge.org

"The whole principle came from the idea that if you broke down everything you could think of that goes into riding a bike, and then improved it by 1%, you will get a significant increase when you put them all together."

Why trials are like bicycles

… but don't rule out radical redesign

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Trials in Surgery

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Trials in Surgery

"Despite rapid growth in recent years, the overall number of randomised controlled trials and systematic reviews in surgical innovations remains small compared with the number of studies evaluating drug treatments."

McCulloch BMJ **2013;346:f3012**

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Systematic review of surgical trials
Wenner *J Am Coll Surg* 2012;215:722-730

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Systematic review of surgical trials
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"More than a third did not identify the trial sponsor…"

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Systematic review of surgical trials
Wenner *J Am Coll Surg* 2012;215:722-730

"More than a third did not identify the trial sponsor…"

"A formal statistical power calculation was reported in only two thirds…"

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Systematic review of surgical trials
Wenner *J Am Coll Surg* 2012;215:722-730

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"15.5% failed to specify the primary endpoint…"

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Systematic review of surgical trials
Wenner *J Am Coll Surg* 2012;215:722-730

"More than a third did not identify the trial sponsor…"

"A formal statistical power calculation was reported in only two thirds…"

"15.5% failed to specify the primary endpoint…"

"10.3% used deterministic allocation sequences…"

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Challenges in surgical trials
Ergina *Lancet* 2009;374:1097-1104

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Ergina *Lancet* 2009;374:1097-1104

- Patients and surgeons may not want to be randomised
- The intervention may be widely available outside the trial
- Sham surgery is controversial, and masking is otherwise difficult

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Challenges in surgical trials
Ergina *Lancet* 2009;374:1097-1104

"We'll just mill around till he's asleep, and then send him back up. This operation is actually for a placebo effect."

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Challenges in surgical trials
Ergina *Lancet* 2009;374:1097-1104

"Few, if any, of these challenges apply only to surgical procedures."

Challenges in surgical trials
Ergina *Lancet* 2009;374:1097-1104

"A more comprehensive approach to studying surgical procedures is needed. This approach should use **patient reported outcomes**, **recorded in real time**, and whenever possible by an **independent observer who is masked to treatment assignment**."

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IDEAL framework

Stages of surgical innovation

1 Idea

2(a) Development

2(b) Exploration

3 Assessment

4 Long-term study

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IDEAL framework
Ergina *BMJ* 2013;346:f3011

Stage 2b: exploration

"One focus of studies at this stage should be to capture **variation in practice**. In addition, careful tabulation of patient characteristics could suggest potential **covariates and confounders**."

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IDEAL framework
Ergina *BMJ* 2013;346:f3011

Stage 2b: exploration

"Observational studies should collect data for **consecutive patients** from **multiple surgeons** (and preferably multiple centres) undertaking the new intervention."

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IDEAL framework
Ergina *BMJ* 2013;346:f3011

Stage 3: assessment

An interrupted time series approach "could fulfil the role of a definitive evaluation when a randomised trial is infeasible."

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IDEAL framework
Ergina *BMJ* 2013;346:f3011

Stage 3: assessment

"Any observational study conducted as an alternative to a high quality, randomised controlled trial should have as many positive design features of such a trial as possible."

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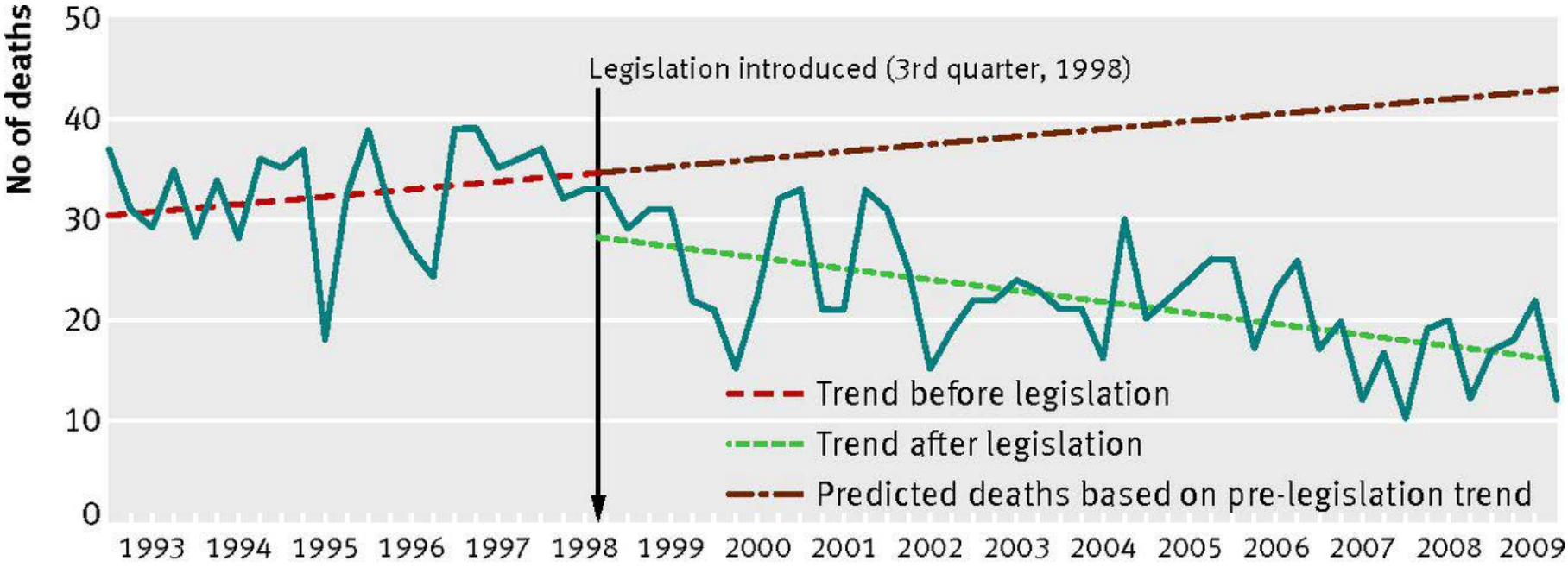
Interrupted time series – typical example

Suicide and open verdict deaths involving paracetamol

Hawton *BMJ* 2103;346:f403



Going back to the IDEAL framework

- **Individual-level data and analysis**
  - adjustment for patient and surgeon factors, secular trends and step changes
- **Patient reported outcomes**
- **Masking of treatment assignment**

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- **Individual-level data and analysis**
  - adjustment for patient and surgeon factors, secular trends and step changes
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Can an ITS do this?

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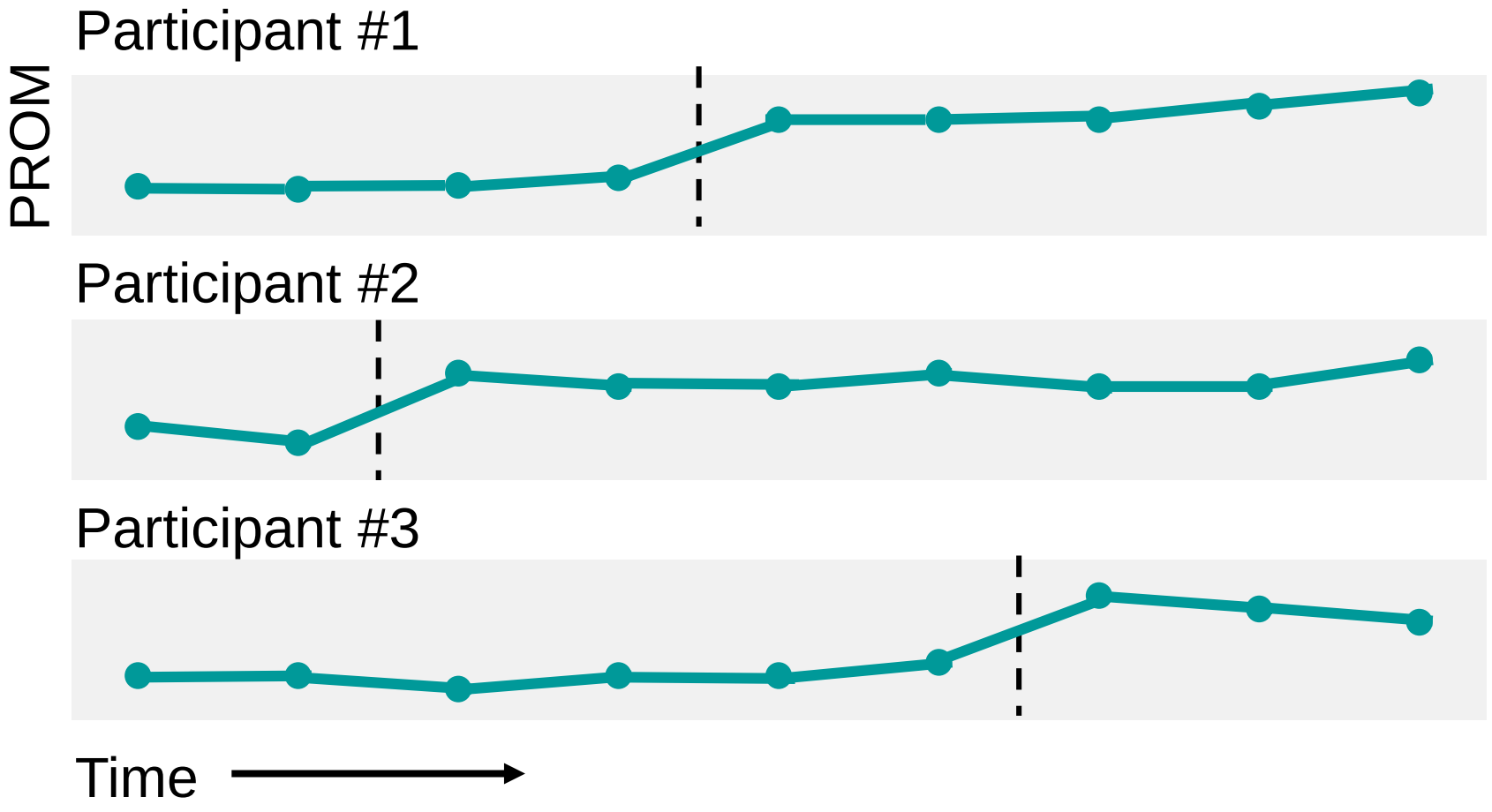
Individual-level interrupted time series



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Agenda for the PROMiSe Workshop

- User acceptability of a platform for electronic informed consent and PROM data capture
- Statistical challenges – beyond “n-of-1”
- Masking and linking to clinical data
- Next steps for applied research