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Statistical challenges

Richard Hooper

Zohra Zenasni, Hanaya Raad, Suzie Cro, Victoria Cornelius, Charles Knowles, Natasha Stevens, Sandra Eldridge

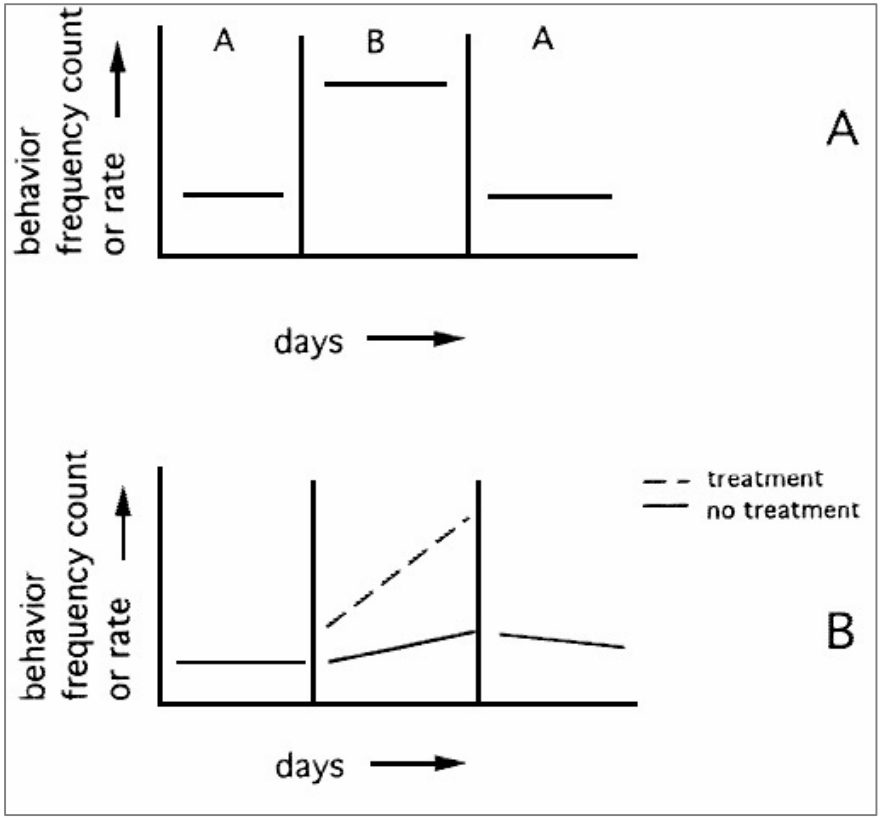
Single-subject designs

Single-subject designs
Backman *Am J Phys Med Rehab* 1999;78:170-6

"They consist of systematic observation, measurement, graphing, and analysis of a carefully defined target behaviour over time and are sometimes referred to as examples of time-series designs."

Single-subject designs

Backman *Am J Phys Med Rehab* 1999;78:170-6



Single-subject designs
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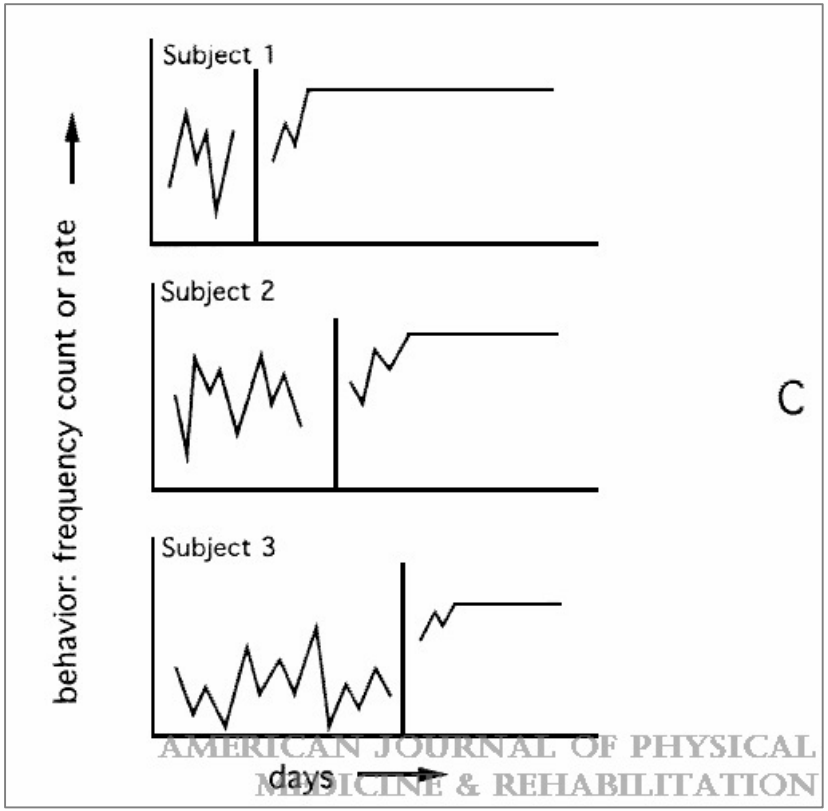

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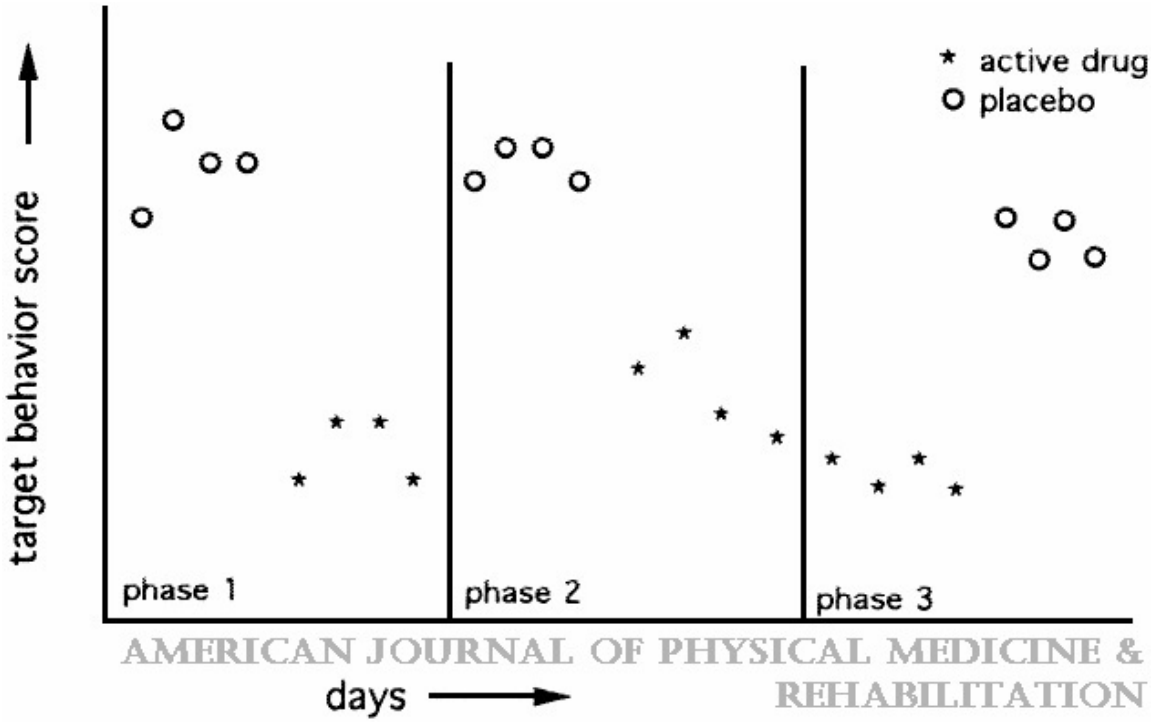

Visual analysis
Backman *Am J Phys Med Rehab* 1999;78:170-6

"The client and clinician can readily observe progress toward the goal and judge whether the intervention plan has an effect. **However, inconsistency among raters relying primarily on visual analysis of graphed single-subject data has been demonstrated**."

Visual analysis
Backman *Am J Phys Med Rehab* 1999;78:170-6

"Visual analysis of graphed data has been the foundation of the analysis of single subject design research studies, but recent studies supplement the analysis with **semistatistical approaches**."

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Behavior Therapy

Volume 6, Issue 5, October 1975, Pages 601-608

On resolving ambiguities of the multiple-baseline design: Problems and recommendations

Alan E. Kazdin, Steven A. Kopel

Show more

https://doi.org/10.1016/S0005-7894(75)80181-X

The multiple-baseline design demonstrates the effect of an intervention by showing changes across separate behaviors (individuals or situations), when, and only when, a treatment intervention is introduced. The design attempts to control for the effect of extraneous events (history) by showing that specific changes are associated with the intervention at different points in time. When the onset of the intervention for one behavior produces *general* rather

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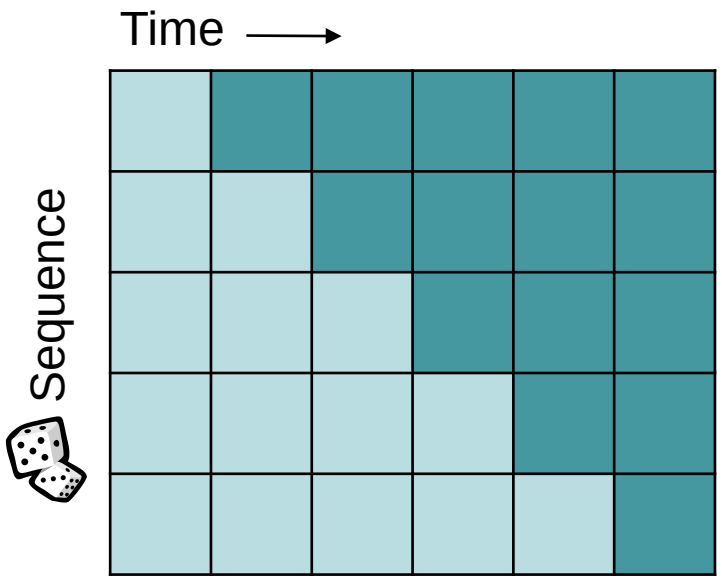
RESEARCH METHODS & REPORTING

The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting

K Hemming,[1] T P Haines,[2] P J Chilton,[1] A J, Girling,[1] R J Lilford[3]

The stepped wedge cluster randomised controlled trial is a relatively new study design that is increasing in popularity. It is an alternative to parallel cluster trial designs, which are commonly used for the evaluation of service delivery or policy interventions delivered at the level of the cluster. The design includes an initial period in which no clusters are exposed to the intervention. Subsequently, at regular intervals (the "steps") one cluster (or a group of clusters) is randomised to cross from the control to the intervention under evaluation. This process continues until all clusters have crossed over to be exposed to the intervention. At the end of the study there will be a period when all clusters are exposed. Data col-



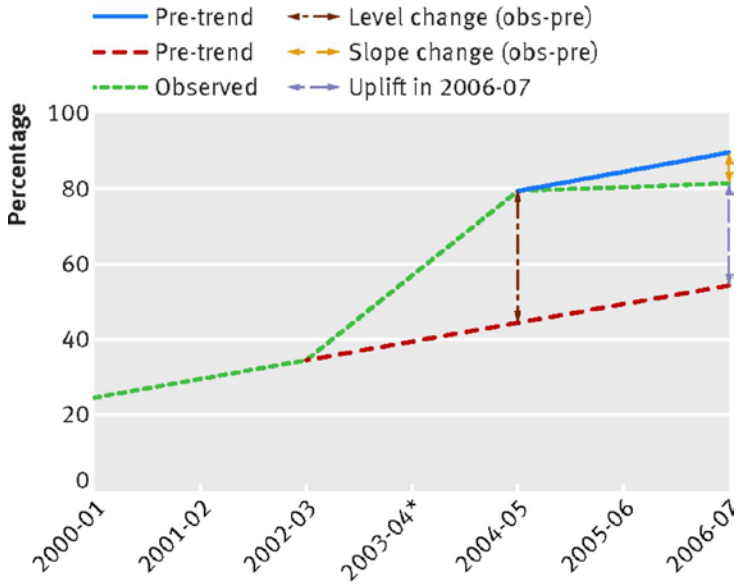
Queen Mary University of London

www.qmul.ac.uk/pctu

Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis

Evangelos Kontopantelis,[1,2] Tim Doran,[3] David A Springate,[2,4] Iain Buchan,[1] David Reeves[2,4]

Interrupted time series analysis is a quasi-experimental design that can evaluate an intervention effect, using longitudinal data. The advantages, disadvantages, and underlying assumptions of various modelling approaches are discussed using published examples



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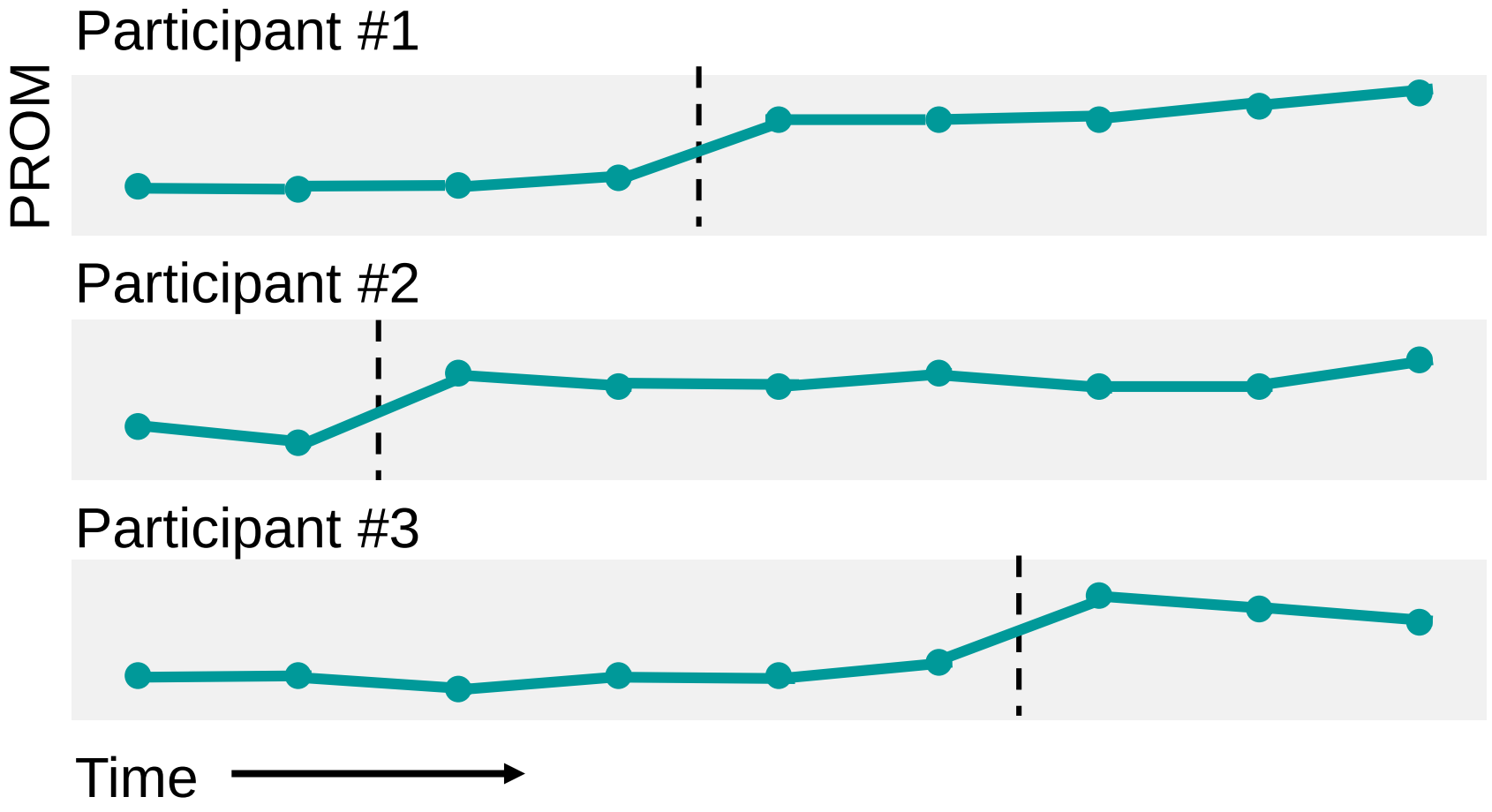
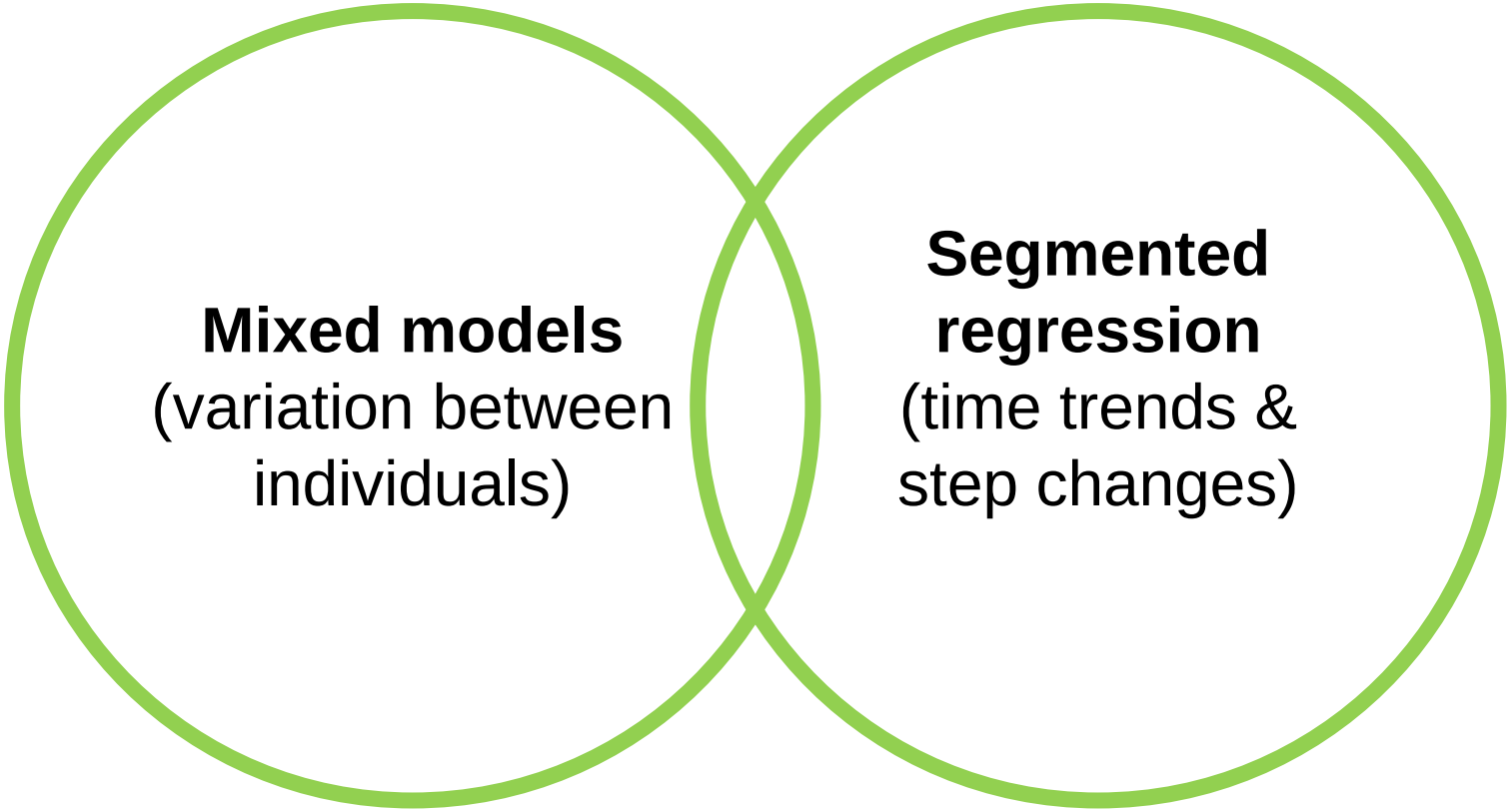
Individual-level interrupted time series



A possible approach to analysis



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Our methodological review

"single subject" studies

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"interrupted time series" studies

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Our methodological review

"single subject" studies

?

"interrupted time series" studies

Our methodological review

((**multi** or **multiple** or "**set of**" or "**series of**") next to ("**single case**" or "**single subject**" or "**n-of-1**" or "**n-of-one**"))

or

((**observational** or **non-randomi?ed** or **nonrandomi?ed**) and "**stepped wedge**")

or

("**multi baseline**" or "**multiple baseline**")

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Our methodological review

Medline
EMBASE
Pubmed
CINAHL
Web of Science
PsychINFO
Cochrane Library

Our methodological review

- Non-randomised evaluations of interventions in humans
- Repeated assessments of the same individuals, including assessments under both the control and intervention conditions
- More than one ‘baseline’
- Target of estimation is the common effect of the intervention

Our methodological review

Full-length, English-language, peer-reviewed, original research articles in one of the following categories:

- Applied research studies or reviews of applied research studies
- Methods papers

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Journal of Clinical Epidemiology 63 (2010) 1312–1323

Journal of Clinical Epidemiology

Individual (*N*-of-1) trials can be combined to give population comparative treatment effect estimates: methodologic considerations

Deborah R. Zucker*, Robin Ruthazer, Christopher H. Schmid

Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University, Boston, MA, USA

Accepted 4 April 2010

Abstract

Objective: To compare different statistical models for combining *N*-of-1 trials to estimate a population treatment effect.

Study Design and Setting: Data from a published series of *N*-of-1 trials comparing amitriptyline (AMT) therapy and combination treatment (AMT + fluoxetine [FL]) were analyzed to compare summary and individual participant data meta-analysis; repeated-measure models; Bayesian hierarchical models; and single-period, single-pair, and averaged outcome crossover models.

Combining N-of-1 trials
Zucker *J Clin Epi* 63 2010;63:1312-1323

"The N-of-1 trial's presumption of individual uniqueness and its goal of personal prediction would seem to contrast with the usual clinical trial objective of identifying a common treatment effect to then apply to each individual in the population."

Combining N-of-1 trials
Zucker *J Clin Epi* 63 2010;63:1312-1323

"Linear mixed models provide great flexibility for meta-analysis, and we investigated a variety of regression covariates and covariance structures as part of our model building."

Combining N-of-1 trials
Zucker *J Clin Epi* 63 2010;63:1312-1323

"We found that under a variety of within-patient covariance structures, the data supported a fixed treatment effect rather than a random treatment effect."

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PLOS ONE

RESEARCH ARTICLE

Understanding Variation in Sets of N-of-1 Trials

Artur Araujo[1], Steven Julious[2], Stephen Senn[1]*

1 Competence Center for Methodology and Statistics, Luxembourg Institute of Health, Strassen, Luxembourg, **2** Medical Statistics Group, School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

* stephen.senn@lih.lu

Combining N-of-1 trials
Araujo *PLoS ONE* 2016;11:e0167167

"A reason to undertake n-of-1 trials could be the efficiency in studying treatments. However, n-of-1 trials are also useful for establishing the personal component of response to treatment."

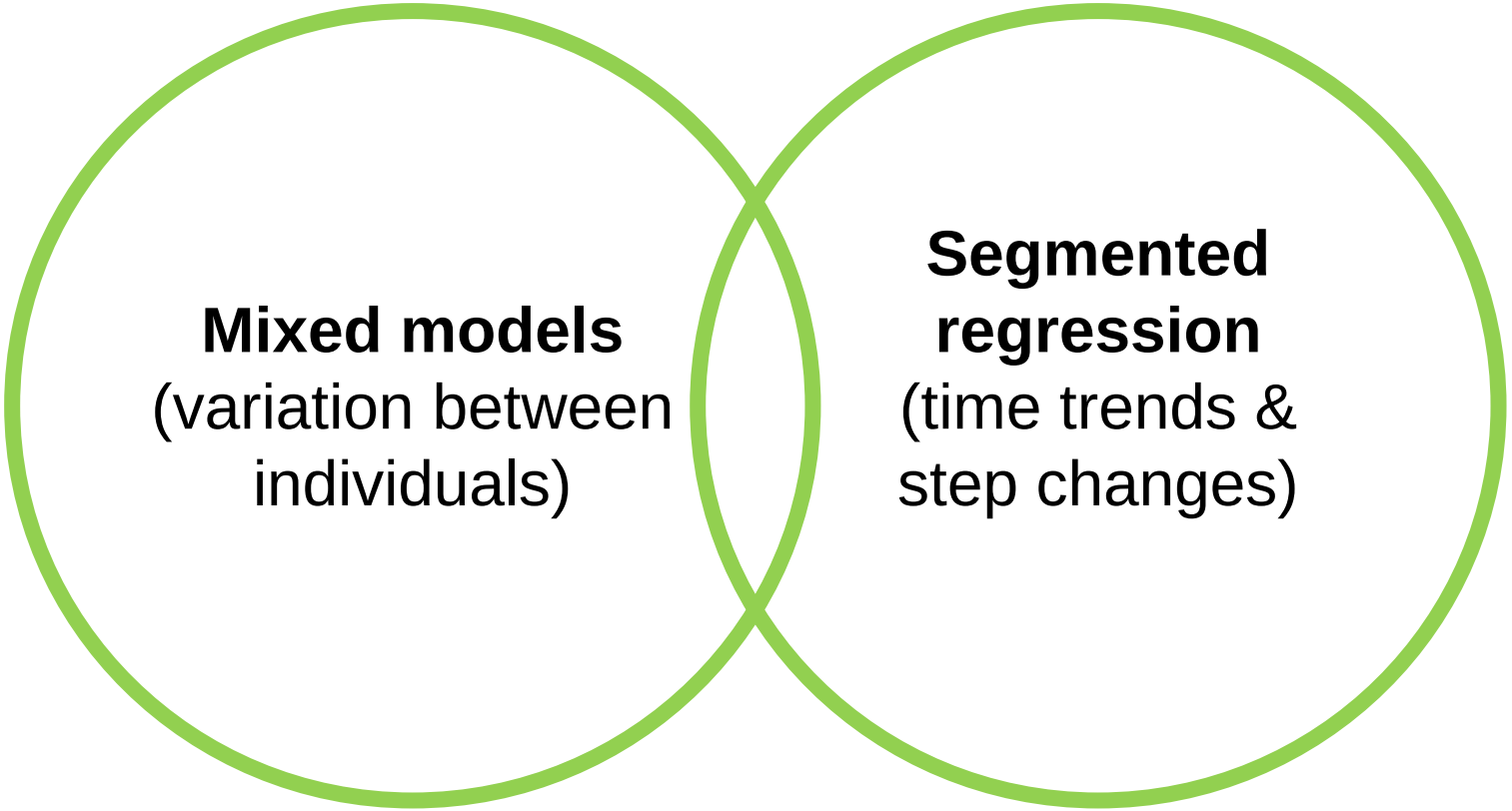
Combining N-of-1 trials
Araujo *PLoS ONE* 2016;11:e0167167

"A common notion in the medical literature is that this will be done individually *ab initio* for each patient. An n-of-1 protocol thus becomes a means of establishing for a given patient, using only results from that patient, what works best for them."

Combining N-of-1 trials
Araujo *PLoS ONE* 2016;11:e0167167

"For the purpose of producing confidence intervals and for the purpose of predicting the effects for future patients a random treatment-by-patient interaction should be allowed for and this is most easily done using a mixed model."

Recap: a possible approach to analysis



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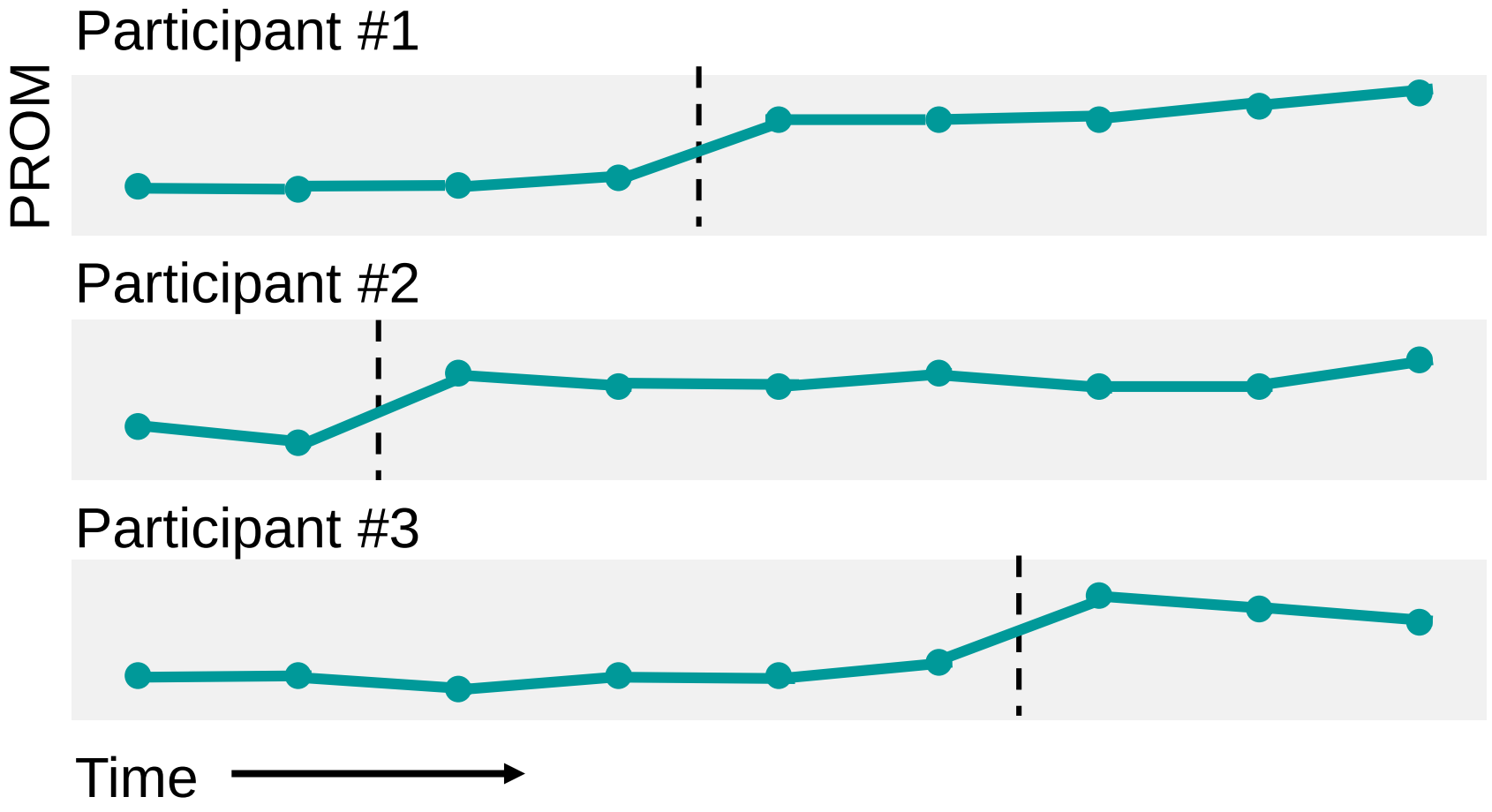
Individual-level interrupted time series



Some methodological challenges

- Balance of ‘baseline’ and ‘follow-up’ data
- Calendar time *vs* time from enrolment
- Is timing confounded by indication?
- Correlation structure and choice of mixed model
- Sample size calculation

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Questions & Comments