
# Time-effect Heterogeneity in Stepped-Wedge Cluster Trials

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## *Presentation Overview*

- Study overview
- Problems faced
- Proposed solutions
- Future work


# Time-effect Heterogeneity in Stepped-Wedge Cluster Trials

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Hospital Falls Trial
• Evaluate intervention aimed at reducing falls (primary outcome) in a single UK hospital
• Rapid response research
• Intervention implementation built around service timetable
• Includes all 36 wards in the hospital
• Partially randomised design
Study Design
Problems

# Study Design

| Group (No. of wards) | Randomised (R)/Non randomised (NR) | Year of study | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2015 | | | | | | | 2016 | | | | | | | | | | | 2017 | | | | | | | | | | 2018 | | | |
| | | J | J | A | S | O | N | D | J | F | M | A | M | J | J | A | S | O | N | D | J | F | M | A | M | J | J | A | S | O | N | D | J | F | M | A |
| 1 (3) | NR | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2 (3) | NR | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 (2) | R | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 (4) | R | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 (5) | R | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 6 (4) | R | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 (4) | R | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 8 (6) | NR | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 9 (5) | NR | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

**Key**

- Control condition, non-randomised ward
- Control condition, randomised ward
- Intervention condition, non- randomised ward
- Intervention condition, randomised ward

# *Problems*

The roll-out was more rapid than planned
- The planned steps in the stepped-wedge component were practically lost

- Wards were very different - so likely to see different time trends and intervention effect

- Only ward level data was available

- Not all wards were randomised
  - Some wards were deemed unsuitable for randomisation


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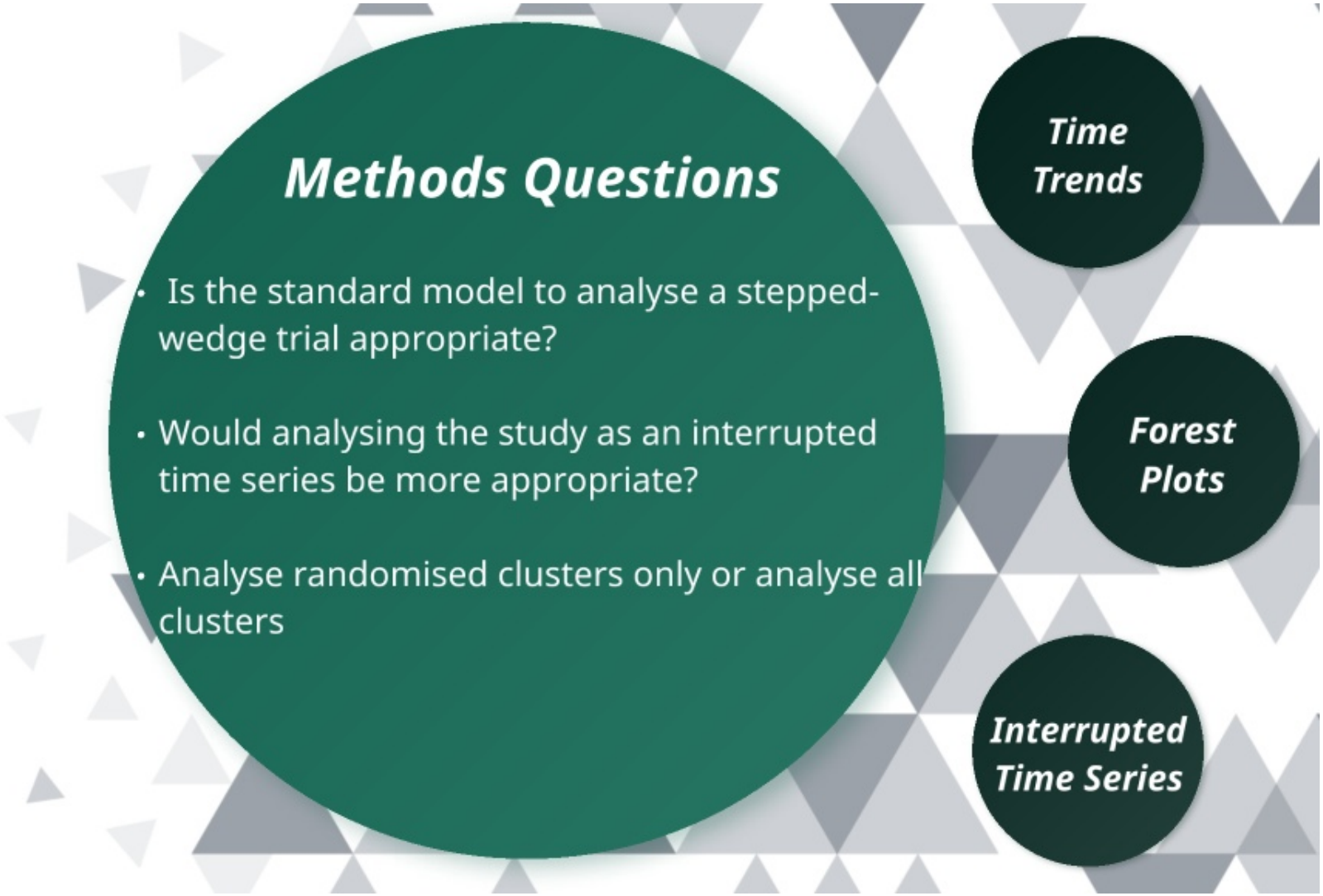
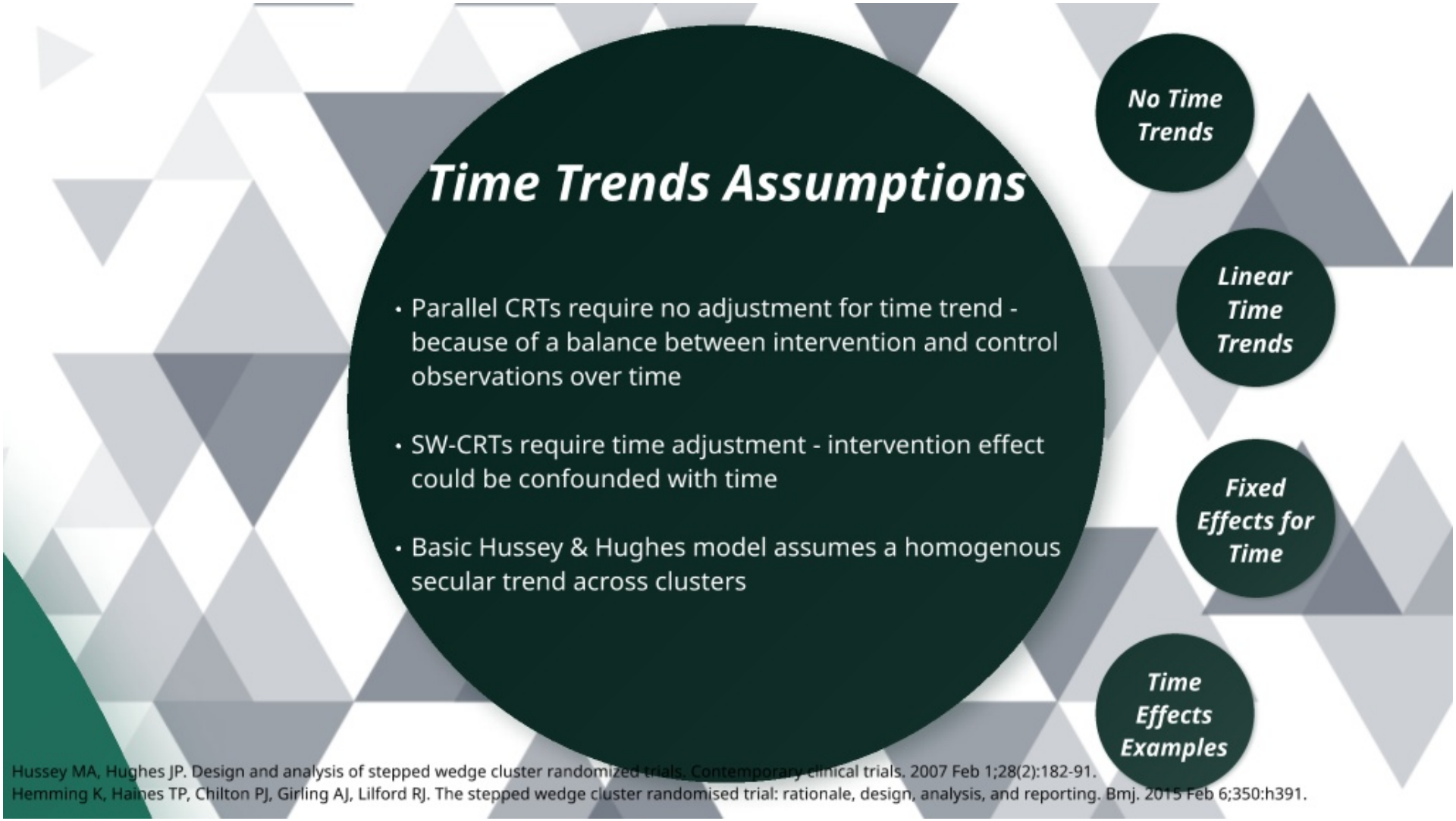
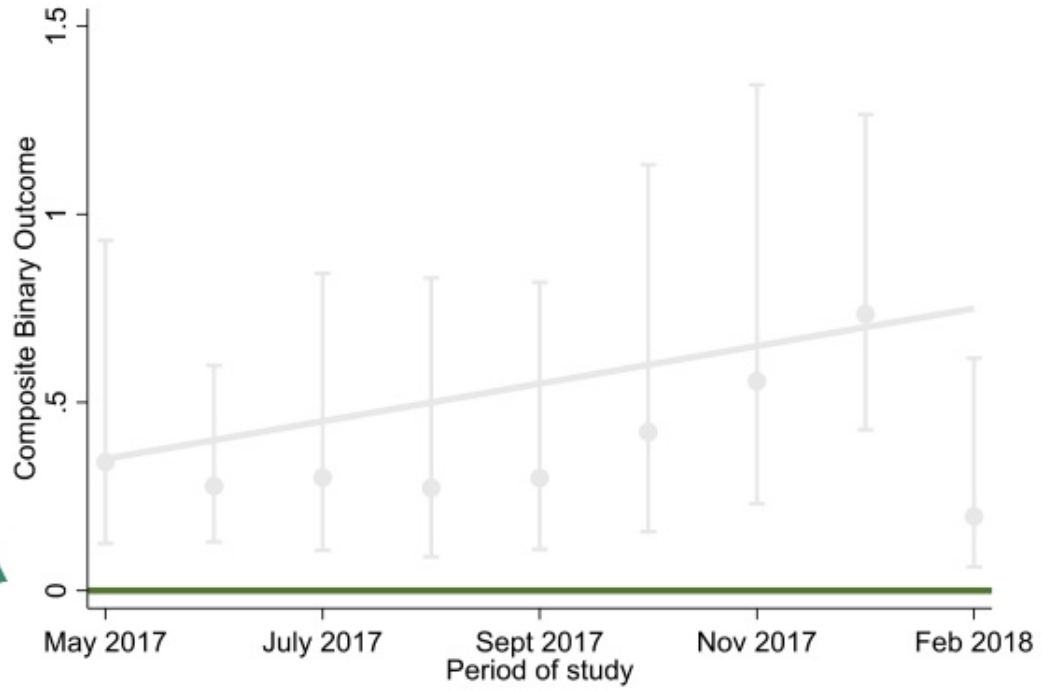

Methods Questions
• Is the standard model to analyse a stepped-wedge trial appropriate?
• Would analysing the study as an interrupted time series be more appropriate?
• Analyse randomised clusters only or analyse all clusters
Time Trends
Forest Plots
Interrupted Time Series




Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemporary clinical trials. 2007 Feb 1;28(2):182-91.
Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. Bmj. 2015 Feb 6;350:h391.

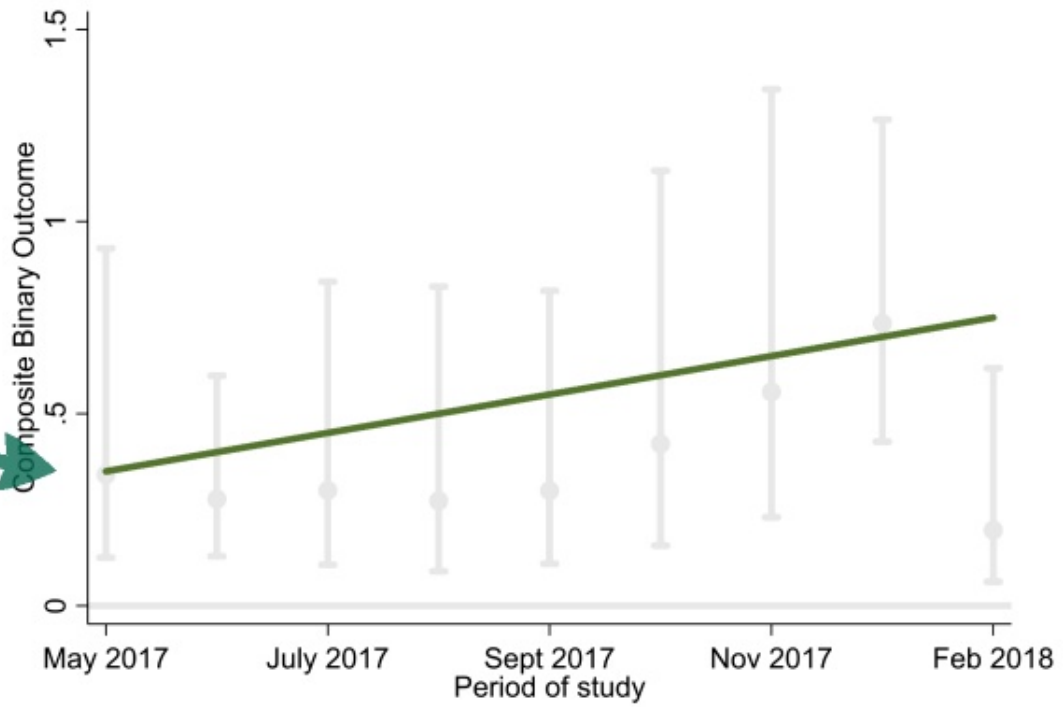
# No Time Trends

- Outcome is not affected by time at all
- As time passes, the outcome is not affected
- Secular trend (or lack of) is identical in all clusters



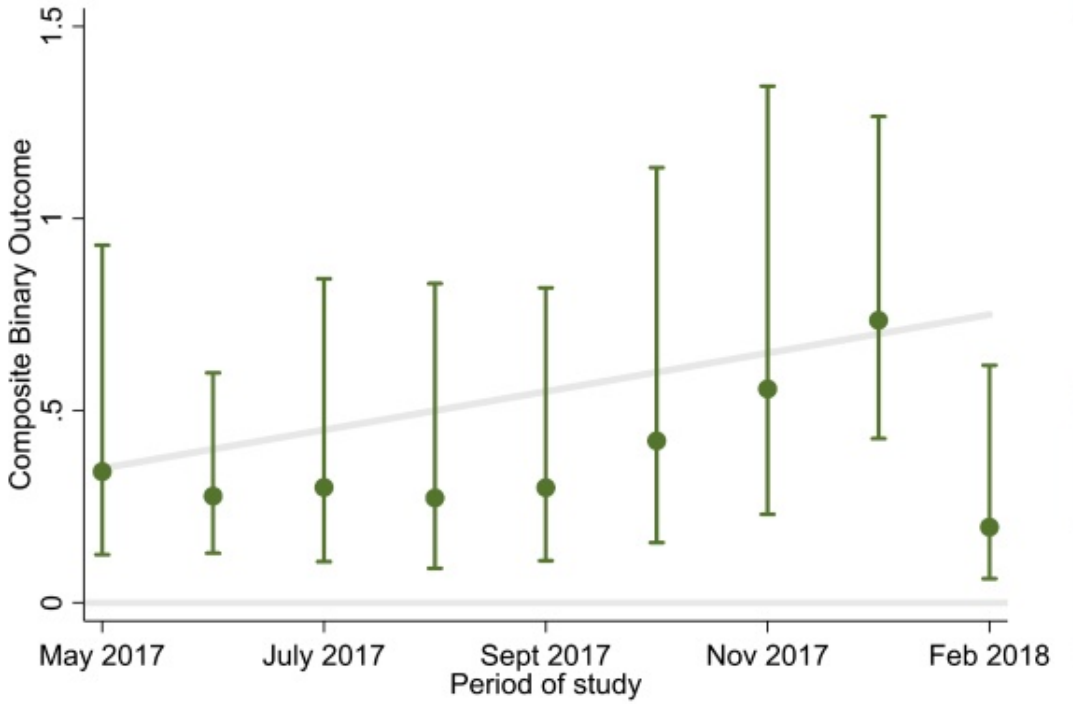
# *Linear Time Trend*

- As time passes, the outcome increases/decreases in a linear fashion
- Secular trend is identical in all clusters



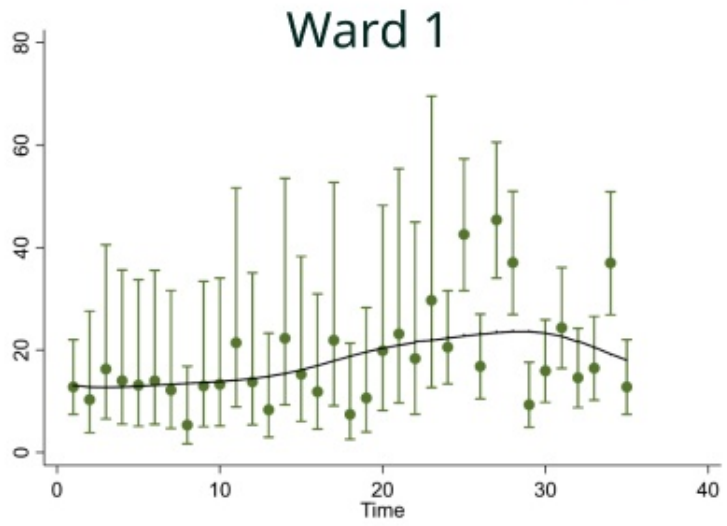
# *Fixed Time Effects*

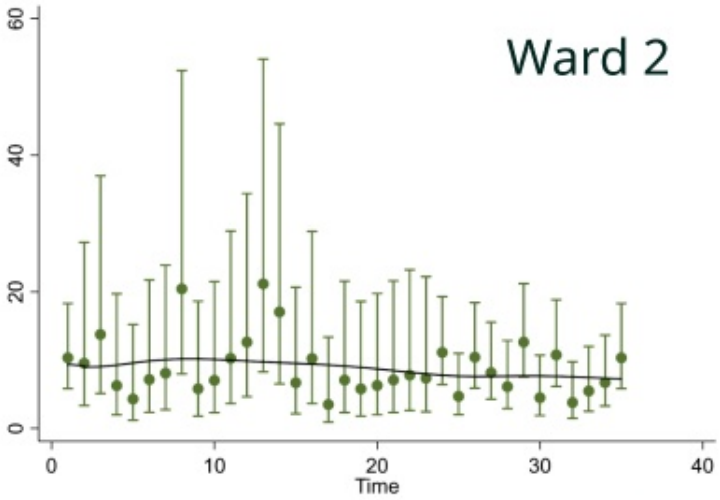
- Modelled as a categorical variable
- As time passes, the outcome could increase or decrease
- Secular trend is identical in all clusters

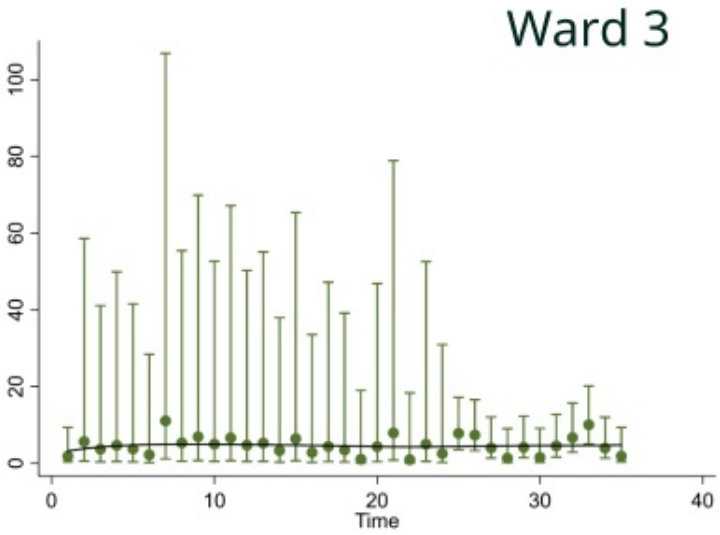


## *Time trends observed in the study*

- Clearly time trends are very different in each ward
- Assumption of the same time trend in each ward would not be valid



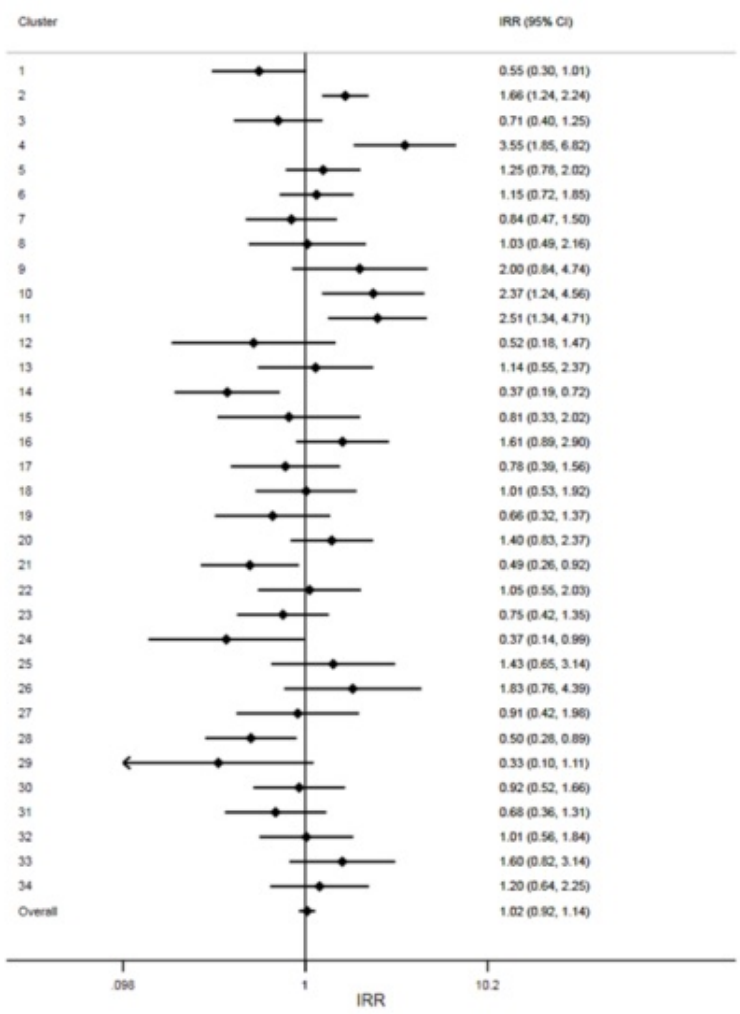
## *Differential time effects & treatment effects*

- Possibility of:
  - Differential treatment effects
  - Differential time effects
- Fitted to each ward individually, a model with:
  - fixed intervention effect
  - time
  - time since intervention

***Immediate intervention effect***

***Time trend***

$$y_{ij} = \theta X_{ij} + \alpha_1 t_{1ij} + \alpha_2 t_{2ij} + e_{ij}$$




# *Immediate Intervention Effect*

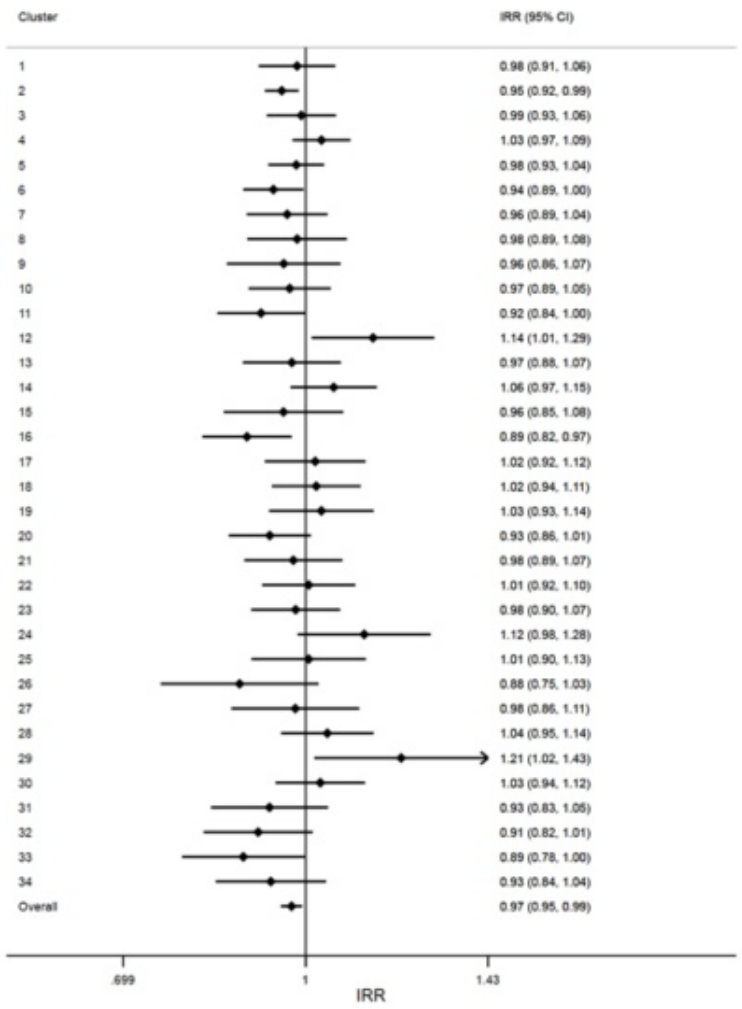
This is the change in primary outcome in month immediately after the intervention

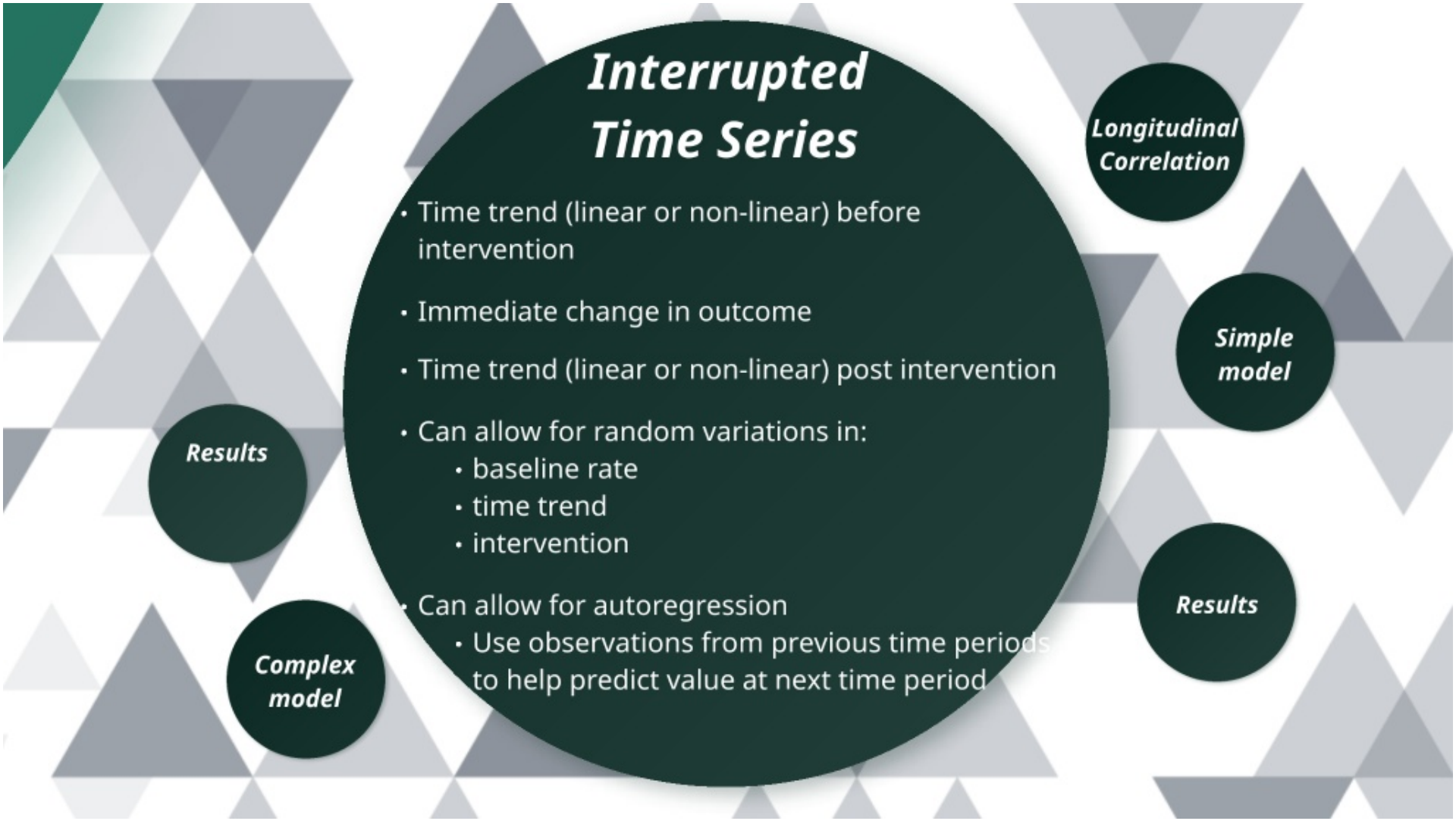
- Large degree of heterogeneity
- Evidence of positive and negative intervention effect
  - Cluster 12 had 63% reduction in falls
  - Cluster 4 had 255% increase in falls

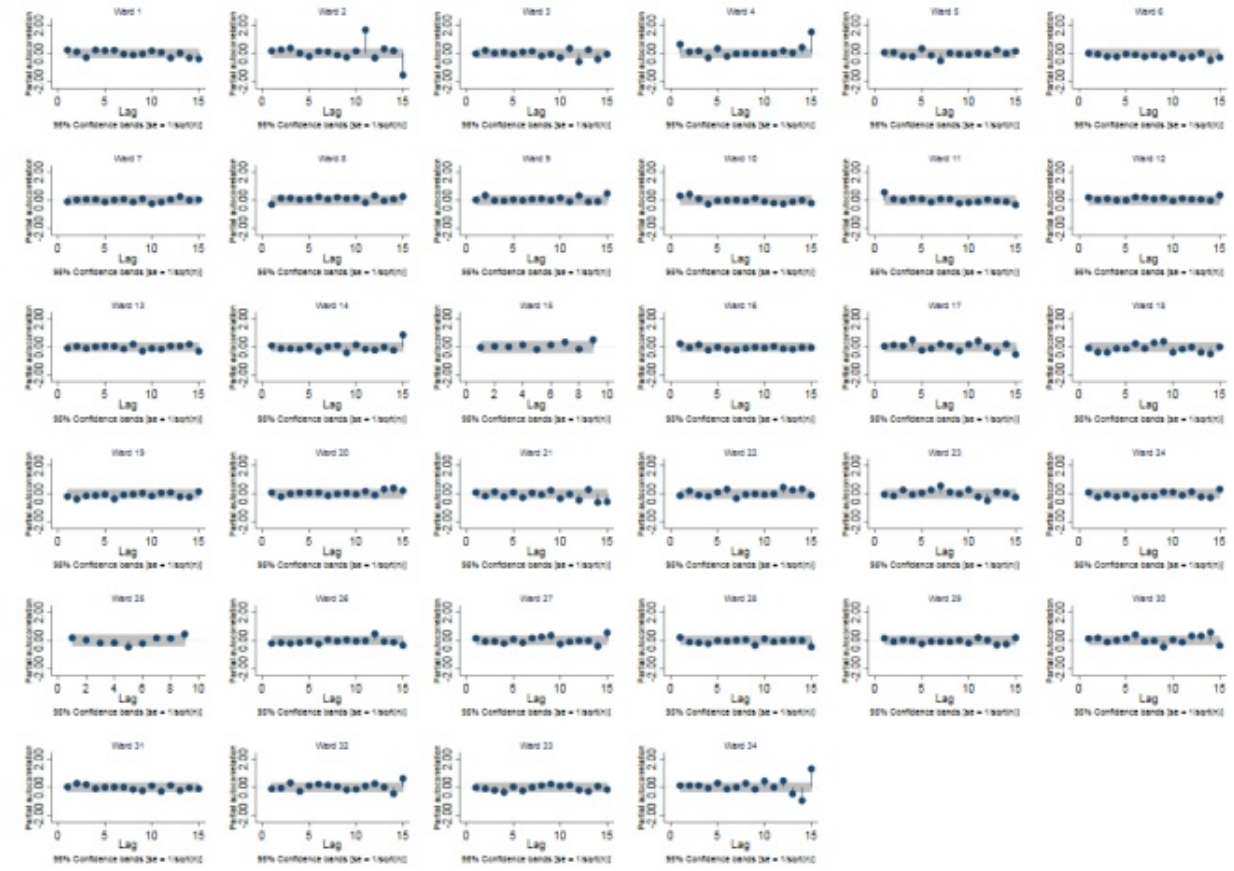
# *Post-Intervention Time Trend*

Time trend in each cluster after the intervention (linear trend - will discuss this more in a moment)

- Some heterogeneity
- Evidence of decreasing and increasing outcome over time

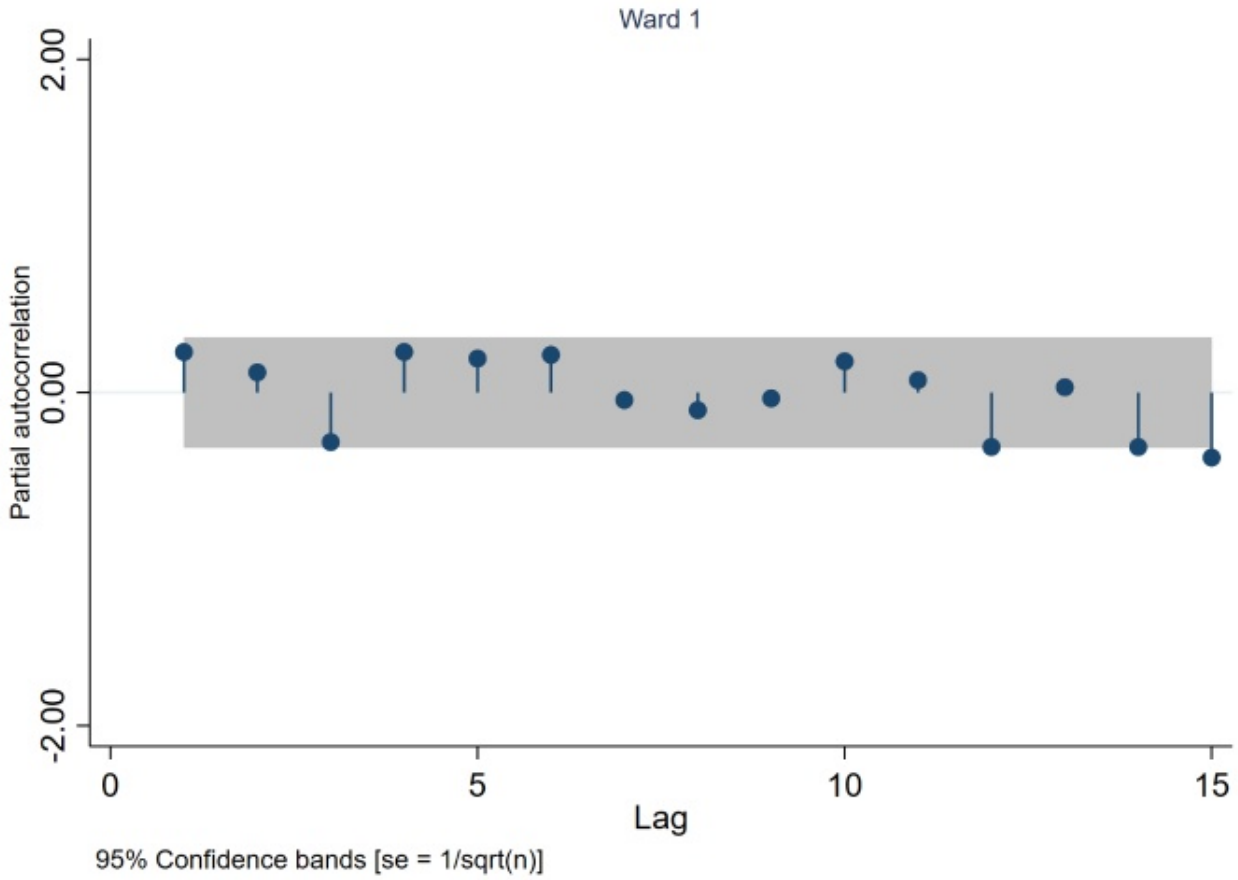



Interrupted Time Series
• Time trend (linear or non-linear) before intervention
• Immediate change in outcome
• Time trend (linear or non-linear) post intervention
• Can allow for random variations in:
• baseline rate
• time trend
• intervention
• Can allow for autoregression
• Use observations from previous time periods to help predict value at next time period
Longitudinal Correlation
Simple model
Results
Results
Complex model



# Longitudinal Correlation

- Auto-regressive models can be fitted that allow for longitudinal correlation
- Checks of the autocorrelation and partial autocorrelation showed (surprisingly) no autocorrelation in this study




## *Partial autocorrelation plot for Ward 1*

- Summary of relationship between an observation in a time series with an observation at an earlier time point.

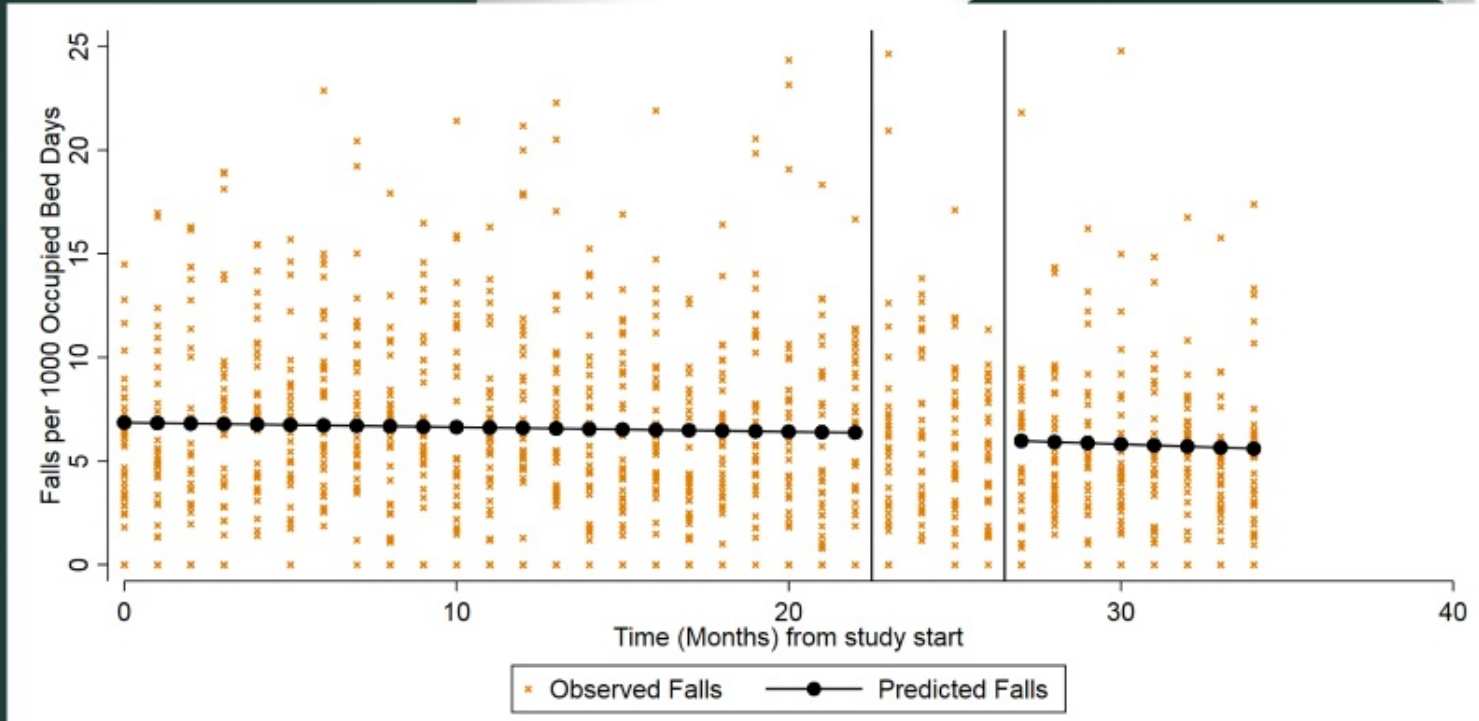
# *Simple model*

Model with

- Random effect for initial rate
  - Allow rate of falls at study start to differ in each ward
- Linear time before  intervention
  - Rate of change in falls is consistent each month
- Random effect for slope pre-intervention
  - Rate of change in falls per month can differ for each ward
- Linear time post intervention
  - Rate of change in falls is consistent each month
- Random effect slope post- intervention
  - Rate of change in falls per month can differ for each ward

# Results

- 6.62 falls per 1000 OBDs in the control phase
- 5.89 falls per 1000 OBDs in the intervention phase
- No evidence of an immediate intervention effect on the rate of falls
- A decrease of approximately 3% in the rate of falls per month after the intervention was introduced



# *Complex Model*

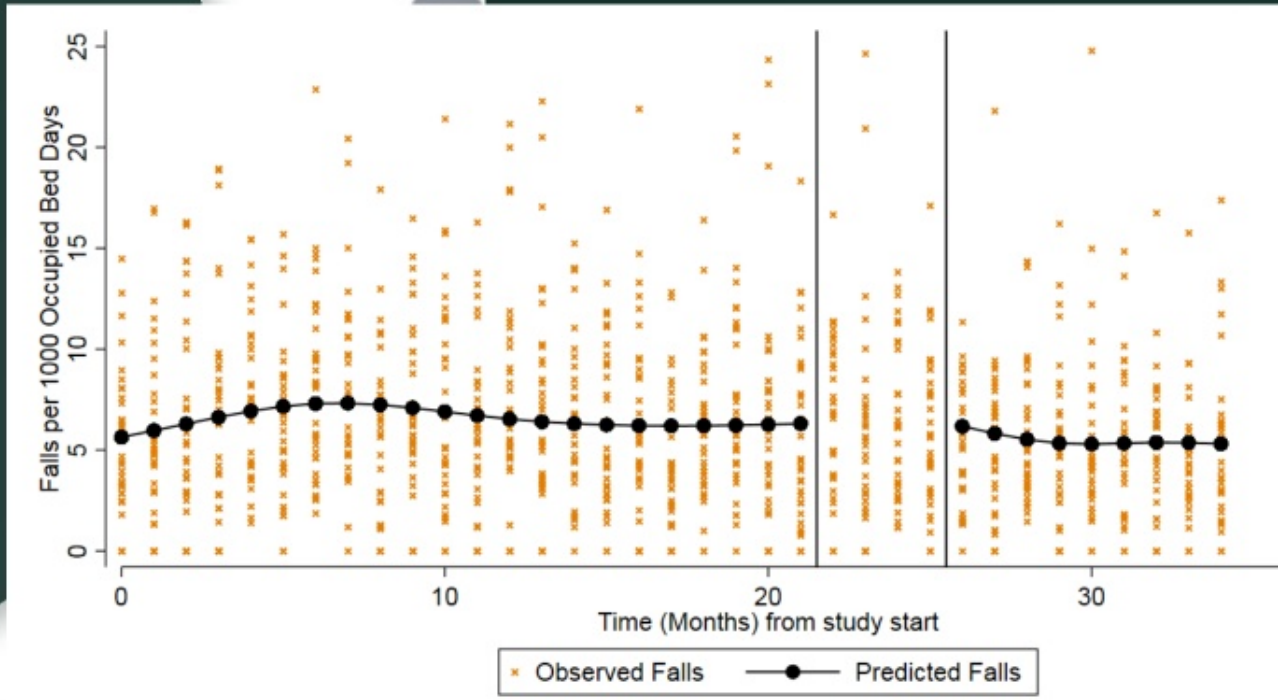
Assumption of linear time trend is a large assumption. In some cases, it may be applicable, but we would not expect it to always be the case.

Rather than assume linear time, it is possible to allow for more complex plots of time.

- In addition to an intervention effect, we fitted a cubic spline to allow for a non-linear time trend. It was possible to allow for:
  - Non-linear time effect pre-intervention
  - Non-linear time effect post-intervention

# *Non-linear Time*

- Interpretation of results can be more difficult
  - No longer simple to describe secular trends
- Not enough evidence of an intervention effect

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## *Time effect heterogeneity in sample size calculations*

How can we allow for variations in secular trends when estimating sample size?

- Current ideas:
  - Simulate IPD with varying secular trends
  - Simulate cluster-level/strata level treatment effects & pool results


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