

# Carryover Effects after Treatment

S. Gwynn Sturdevant, University of Auckland  
with support from Dr. Thomas Lumley, and Dr. Ross Ihaka

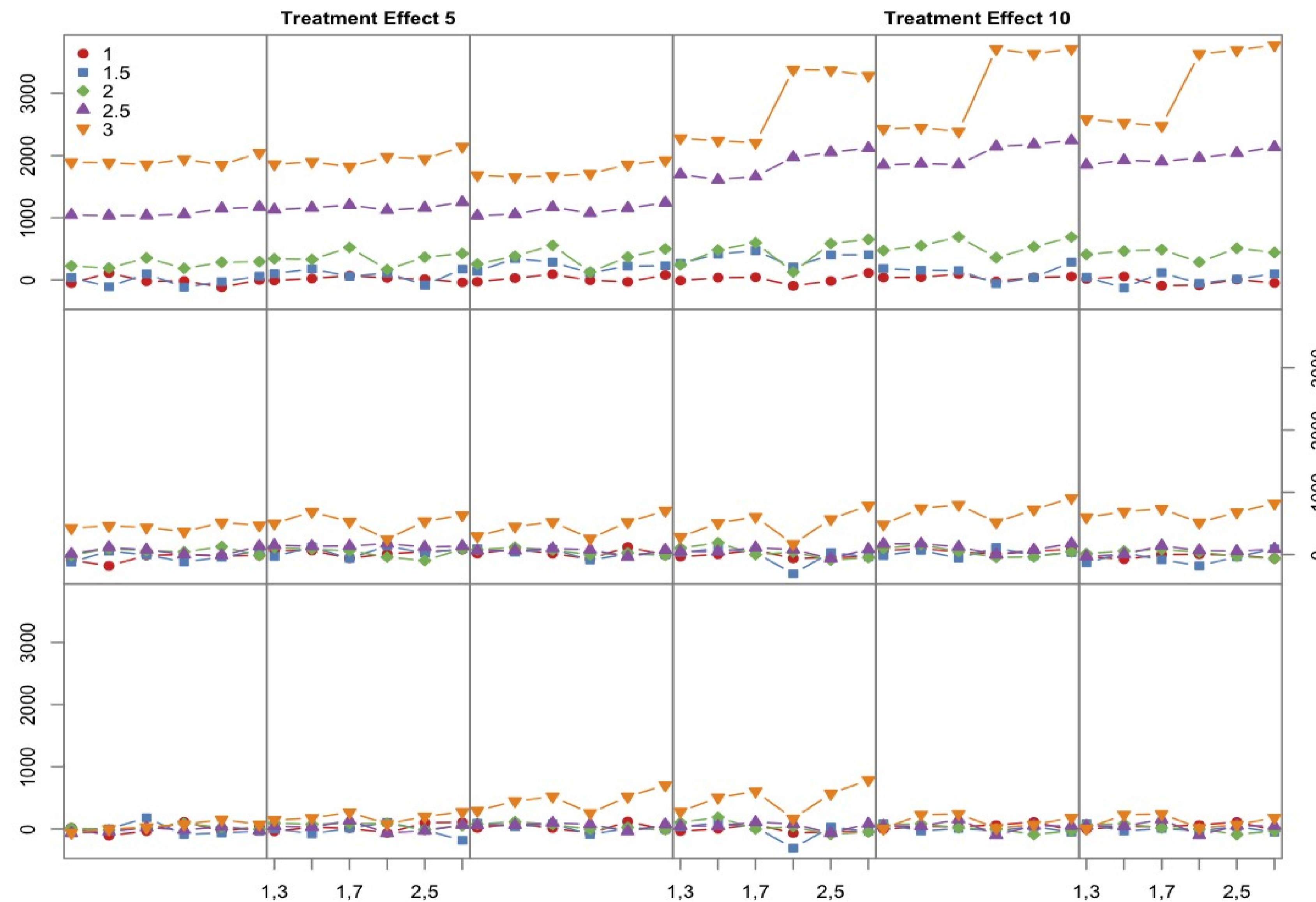
## Introduction

- Historically, randomised controlled trials test treatments for diseases
- New genre of analyses - **postpone** the onset of condition through treatment
- How can we test for carryover effects?
- Two studies
- TROPHY - TRial of Preventing Hypertension, inadequate design
- DREAM - Diabetes REDuction Assessment with ramipril and rosiglitazone Medication, inadequate design
- TROPHY - **fallible** design
- In TROPHY subjects randomised to candesartan or placebo for 2 years
- Participants were measured every three months to determine hypertension
- Hypertension - **3** measurements above the threshold of 140 mm Hg
- Placebo group 63.0% and the treatment group 53.2%
- Need **robust** methods with which to test a carryover hypothesis.

## Simulation

- Simulating (BP)
- Random number between 125 - 140 mm Hg
- Trends of 0, 1, or 2 mm Hg per year
- Standard errors of 3, 5, and 7 mm Hg
- Treatment effects were 0, -5, and -10
- Measurement times either every 3 months, 6 months, or yearly.
- Duration of the treatment was either 1, 1.5, 2, 2.5, or 3 years
- 6 Rules for diagnosis
  - one measurement above
  - two consecutive measurements above
  - average of 2 consecutive measurements were above
  - 3 measurements over
  - Average of 3 consecutive measurements above
  - 1 over then remove standard error to confirm diagnosis
- Carryover of 0, 1, and 2 years

## Apparent Treatment Effects



## Graph

- Based upon 1 over then removal of standard error
- End of treatment time - largest impact upon carryover
- End of treatment times - 1, 1.5, 2, 2.5, and 3 years
- Rows are
  - Top - carryover of 2 years
  - Middle - carryover of 1 year
  - Bottom - carryover of 0 years
- Y axis is measurement of differences between treatment & control of hypertensive free

- Columns indicate frequency of measurement (L to R)
  - Every 3 months
  - Every 6 months
  - Every year
  - Every 6 months
  - Every 3 months
- X axis is trend, standard error
  - Trend 1, standard error 3
  - Trend 1, standard error 5
  - Trend 1, standard error 7
  - Trend 2, standard error 3, ...

## Results

- Carryover of 2 - most detectable
- Trend impacts upon carryover most when treatment effect is 10
- Smaller carryovers almost negligible when treatment effect is 5, except when 3 year treatment length
- Longer treatment time - more it looks like carryover
- Higher chance of finding carryover in treatment length 2.5 years and 3 years
- No analysis where yearly trend is 0 as
  - BP starts out less than 140 mm Hg
  - Trend 0 mm Hg per year
  - Removal of error in the rule
  - Results in diagnosis of nil
- Graphs have an m shape with less difference when error is 3 then climb again
  - Gradient larger as trend increases - second half of m - steeper
- When length of treatment - large, measurement - yearly, we have small false positives
- Treatment larger - less people diagnosed

## Further Research

- Big difference due to trend when carryover above 2, treatment 10, 3 year treatment - Why?
- Trend 2, treatment effect 3 causes big dip - Why?
- Test for **interactions** with carryover using this rule
- More ability to detect when carryover is 1, treatment time < 3 yr
- Analysis of 5 other rules, variables, and their interactions