Statistical Modeling of Carryover Effects After Cessation of Treatments

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TROPHY

Trial Of Preventing HYpertension

- 809 participants with systolic blood pressure (BP) 130 - 139 mm Hg randomised
- Treatment - two years, then two year follow up
- Placebo - 4 years of monitoring
- Measurements every 3 months
- 69% of those diagnosed with hypertension did so by having 3 measurements above 140 mm Hg
- Treatment 53.2%, Placebo 63.0% cumulative diagnosis
- Concluded that “the effect of active treatment on delaying the onset of hypertension can extend up to 2 years after the discontinuation of treatment. “

Criticisms of TROPHY

Lumley, Rice and Psaty (2008)

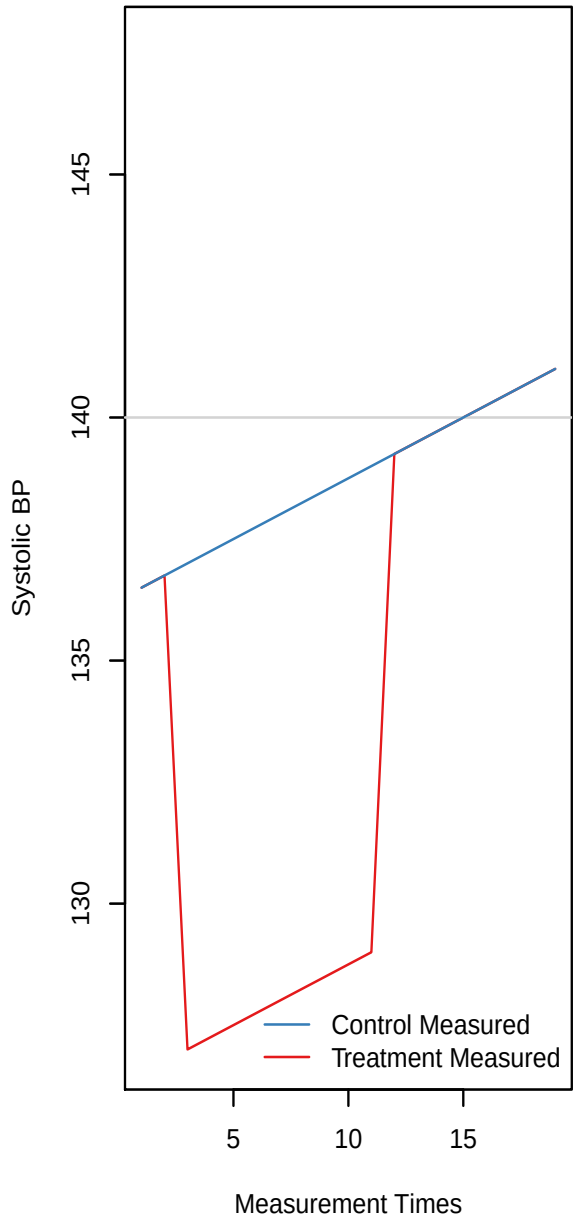
- Simulations conducted to replicated TROPHY outcomes
- Without carryover, similar cumulative incidences of hypertension were found in 80% of studies
- Suggest that this is an interesting question

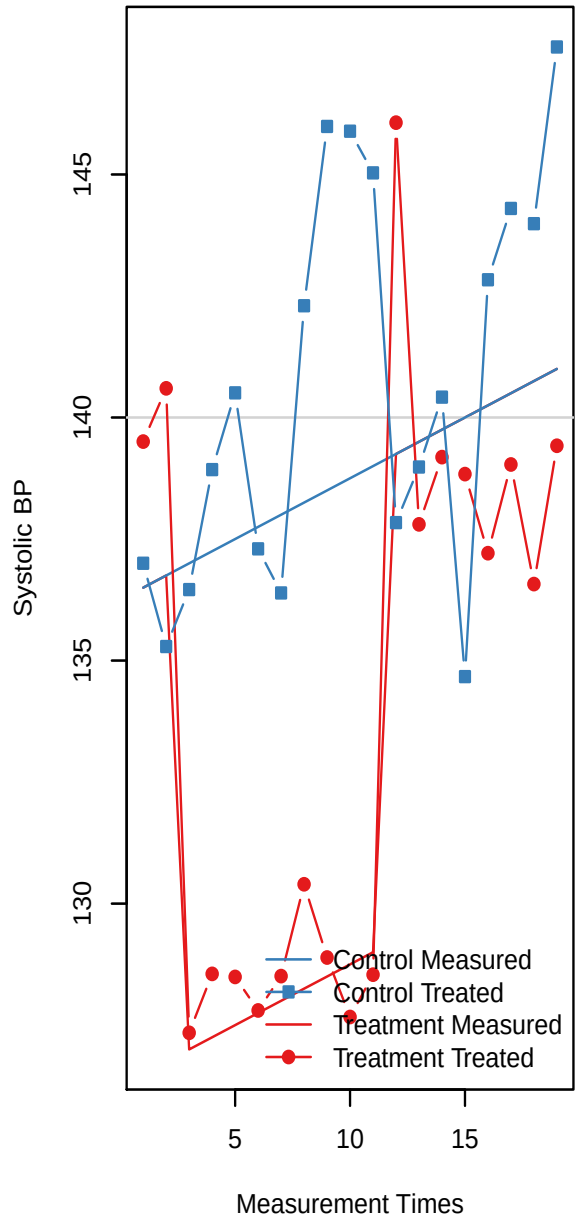
Persell and Baker (2007)

- "Does temporary treatment alter the subsequent course?"
- Cumulative diagnosis rates would differ even with identical underlying BP

Meltzer (2006)

- Post hoc changes of language
- Unpublished data


Systolic BP
130
135
140
145
5
10
15
Measurement Times
Control Measured
Treatment Measured


Systolic BP
130
135
140
145
5
10
15
Measurement Times
Control Measured
Control Treated
Treatment Measured
Treatment Treated

Comment

Due to random variation, throughout treatment we have more values above the threshold in the control arm of the study than the treatment arm. Thus 80% of studies designed similarly and without carryover will have differences in cumulative diagnosis rates.

Applications

Why should we care?

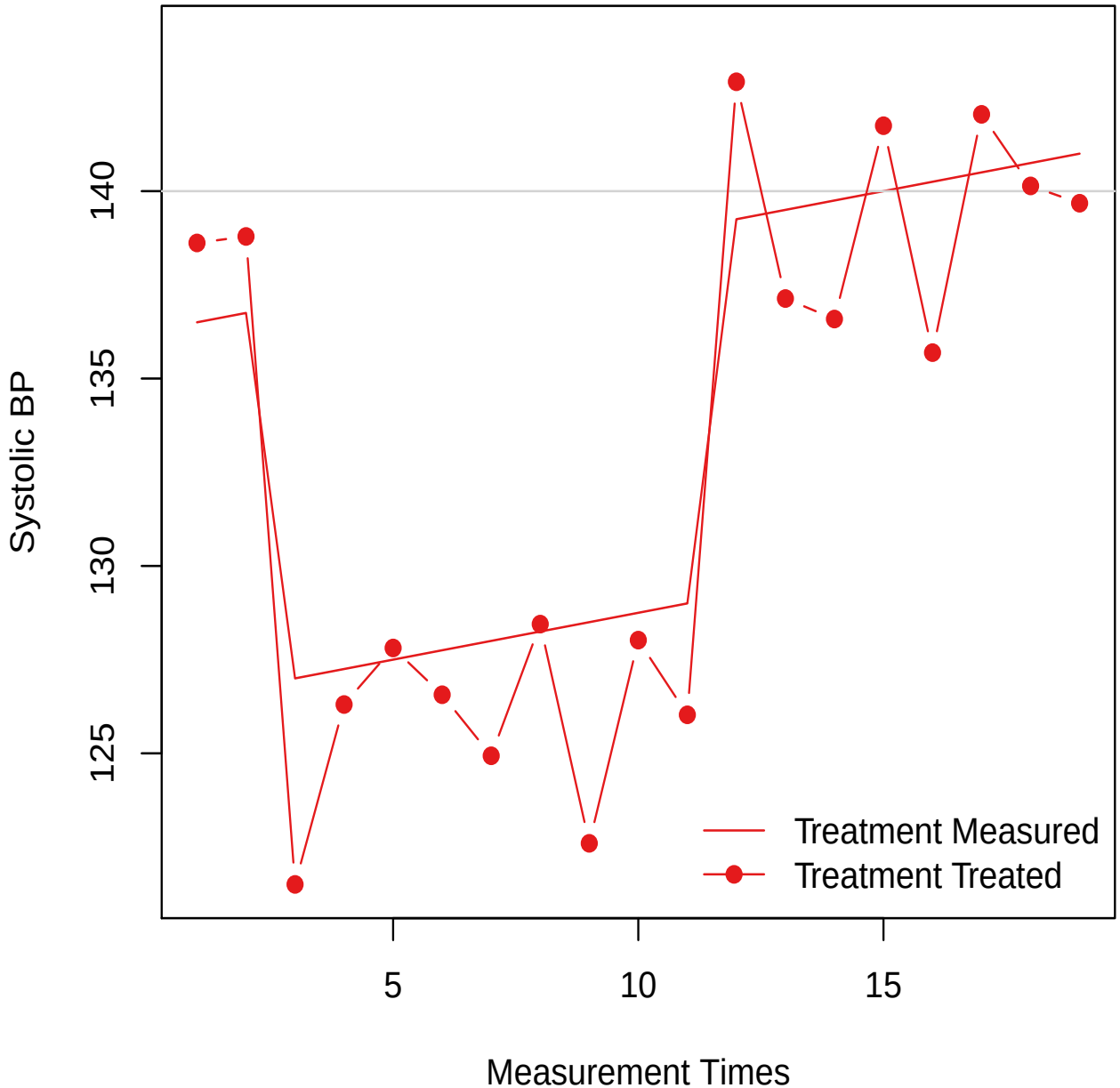
- Diabetes REduction Assessment with ramipril and rosiglitazone Medication - treating prediabetes
- Therapeutic interventions - diet and exercise
  - Teach them about healthy eating - is there a long-term impact?
  - Boot camp at 5am
  - Yoga retreat
  - Meditation retreat
  - Naturopath
  - Hearing the Dalai Lama speak
  - Ballroom dancing

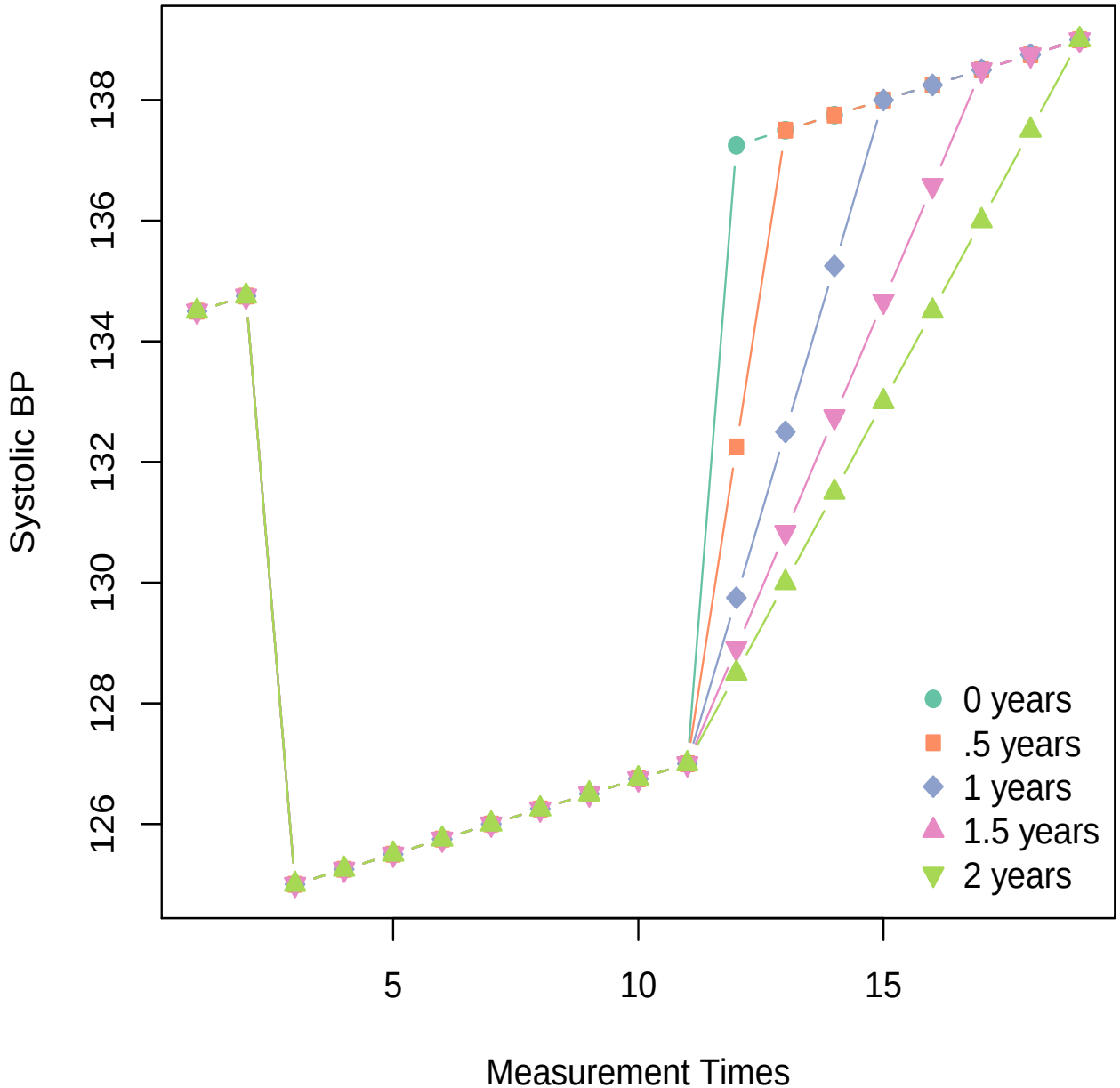
Rules for Diagnosis

Six Rules

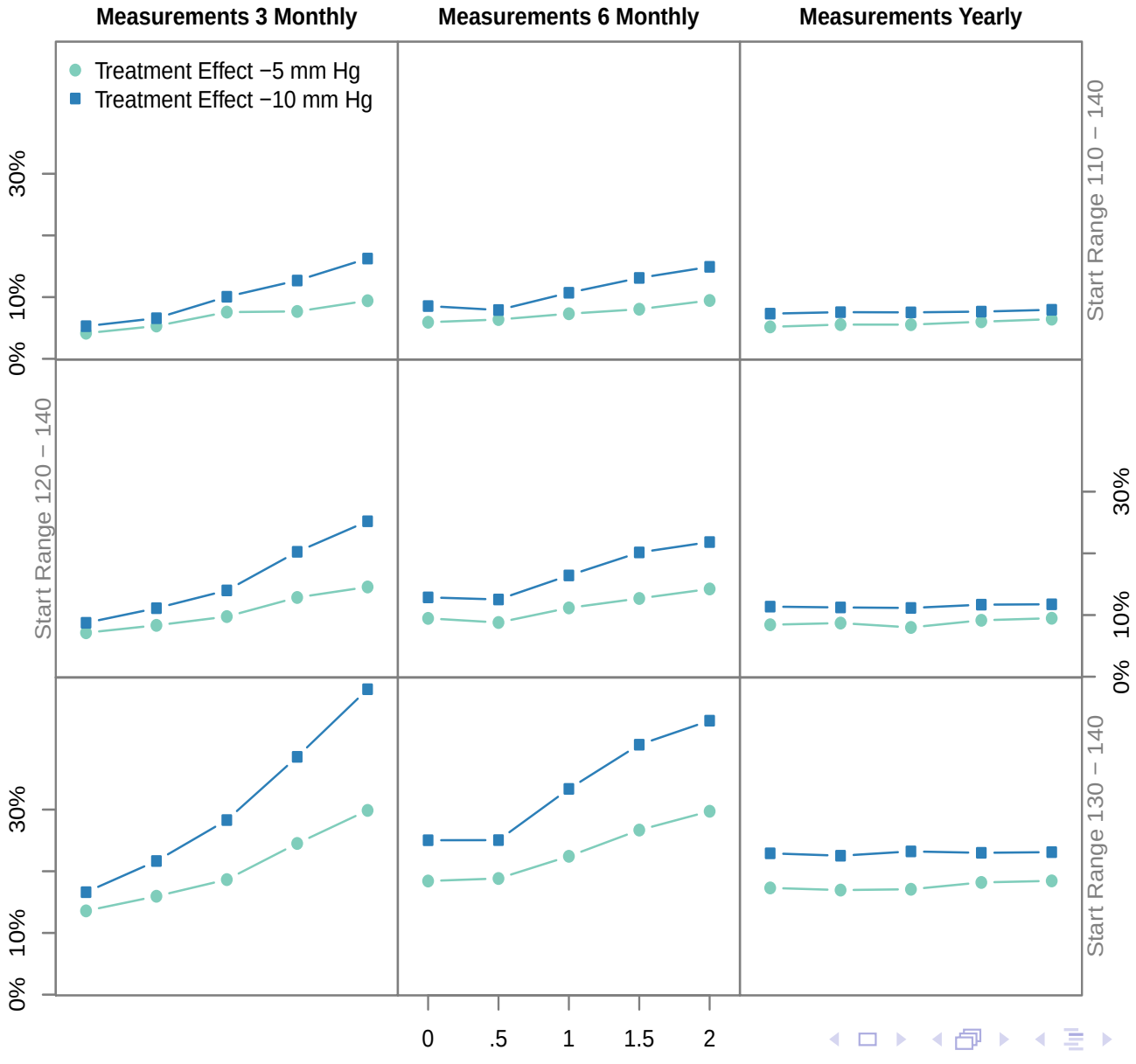
- 1 Over
- 1 Over Then Check
- 2 Consecutive
- Average of 2 Consecutive Measurements
- 3 Measurements Over
- Average of 3 Consecutive Measurements Over

We test the rules to see which have might have appropriate differences and powers.

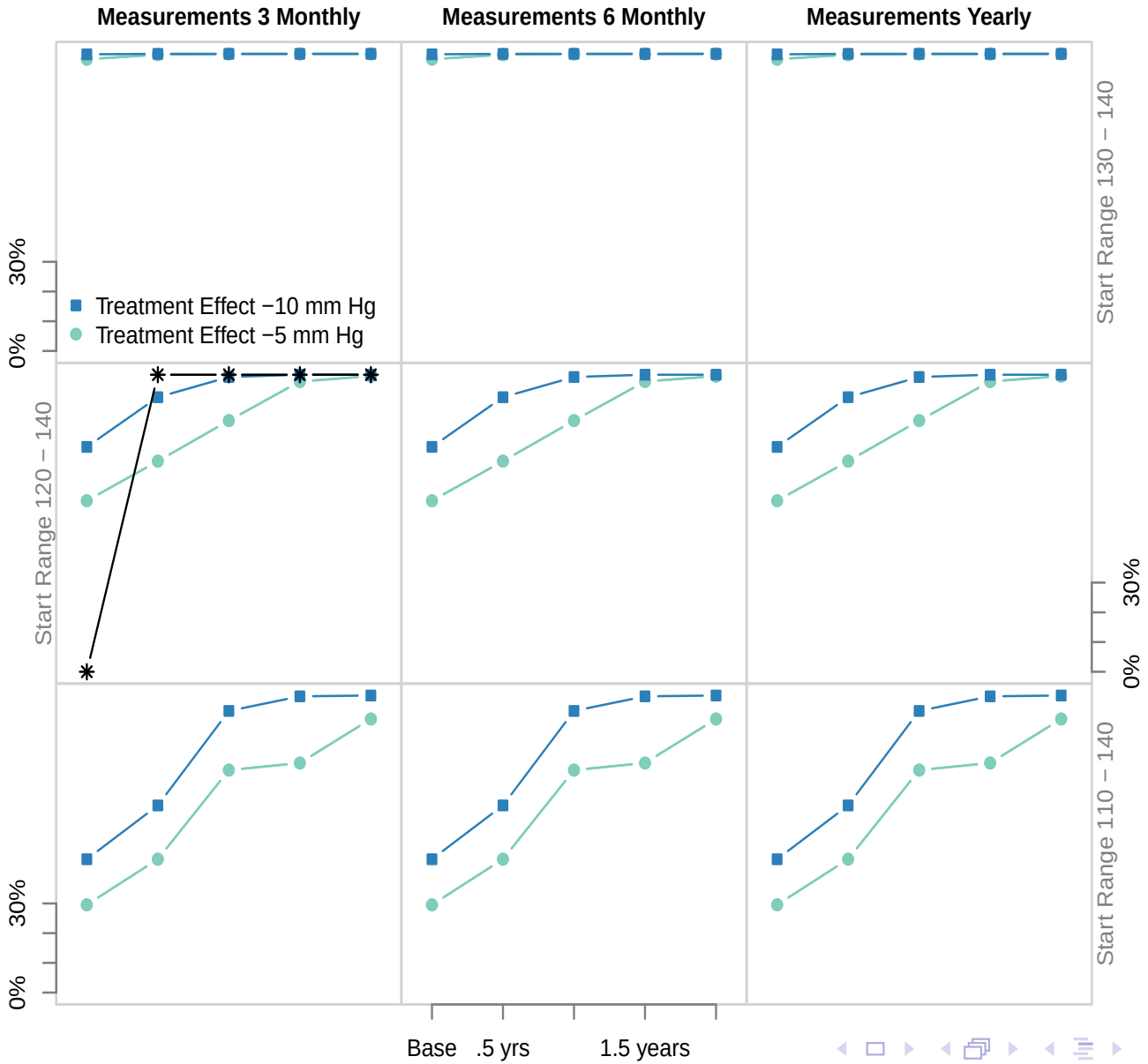

Systolic BP
125
130
135
140
5
10
15
Measurement Times
Treatment Measured
Treatment Treated


Systolic BP
126
128
130
132
134
136
138
5
10
15
Measurement Times
0 years
.5 years
1 years
1.5 years
2 years

Apparent Treatment Effects Rule 3 Over Varying Start Range



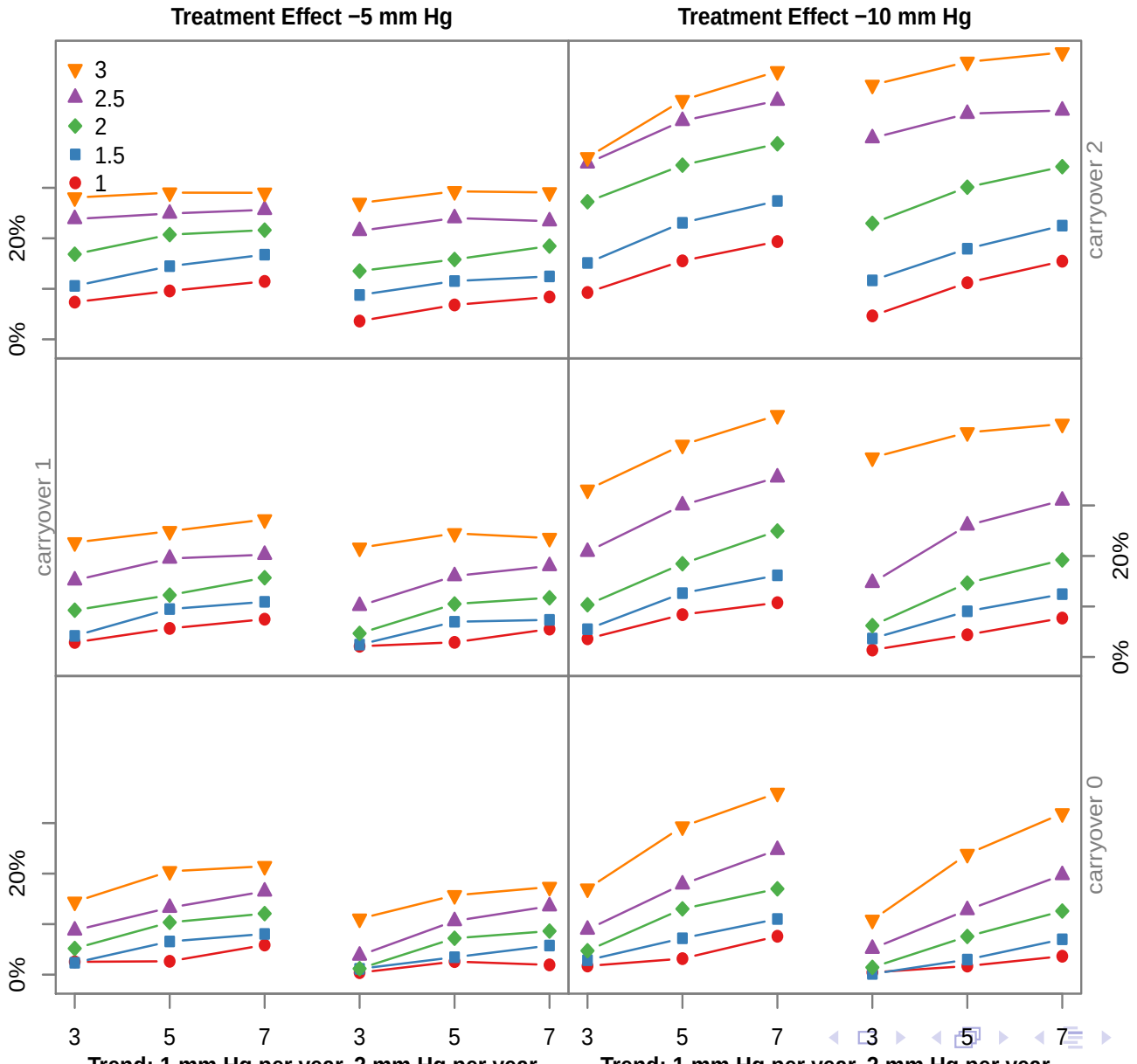
Estimated Powers: Rule 3 Over Varying Start Range



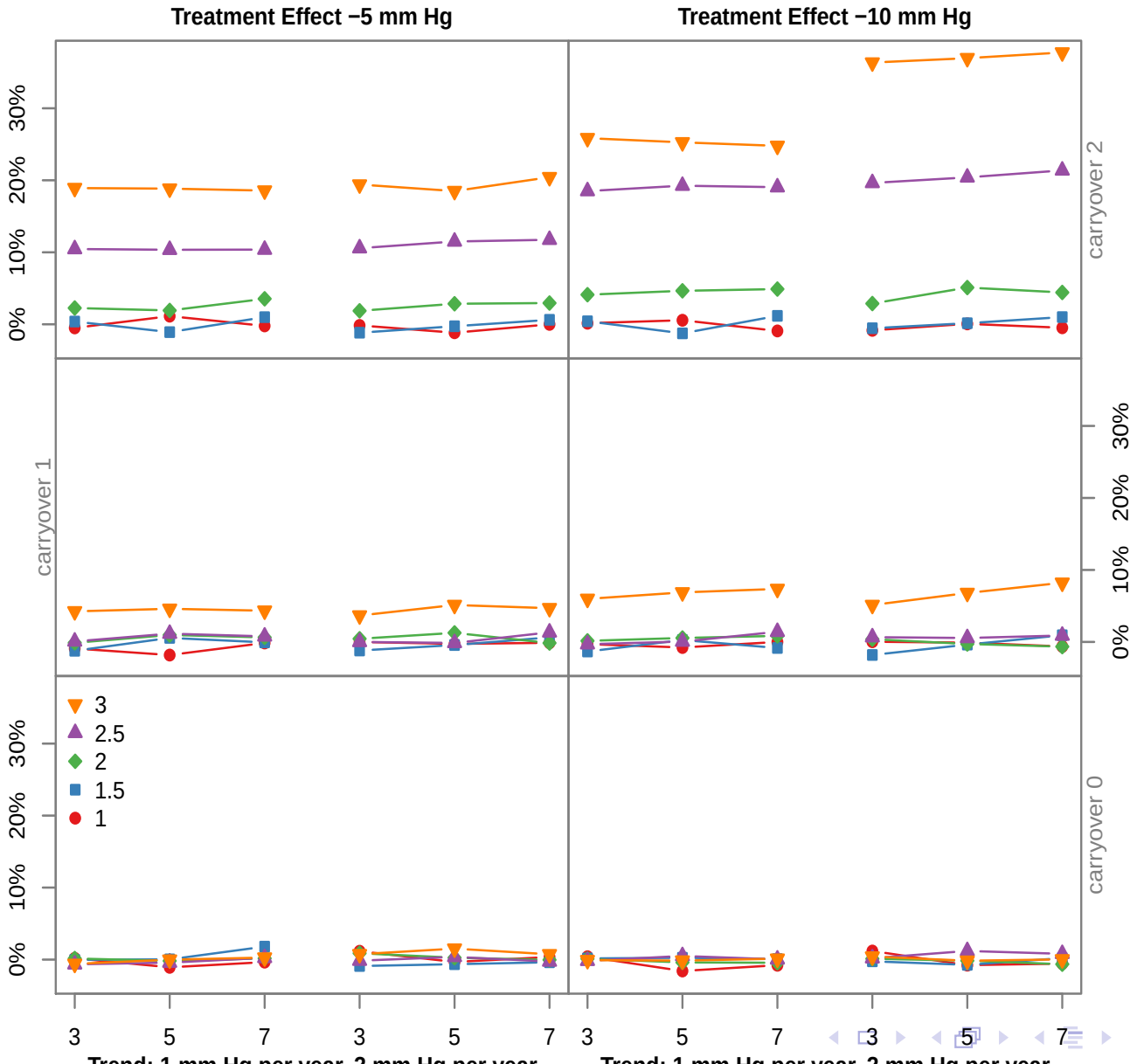
ANOVA

Completing an analysis of variance for a least squares model suggests that the variable with the highest impact upon the difference between treatment and control arms, which could be chosen, was the length of time that the treatment was taken. The longer the time that systolic BP was artificially lowered using medication the more likely we are to find a true carryover, if a true carryover exists. The F-Statistic was 4548.6 on 4 df. Note that the ANOVA was completed for rule 1 over then check and treatment effect -5 mm Hg.

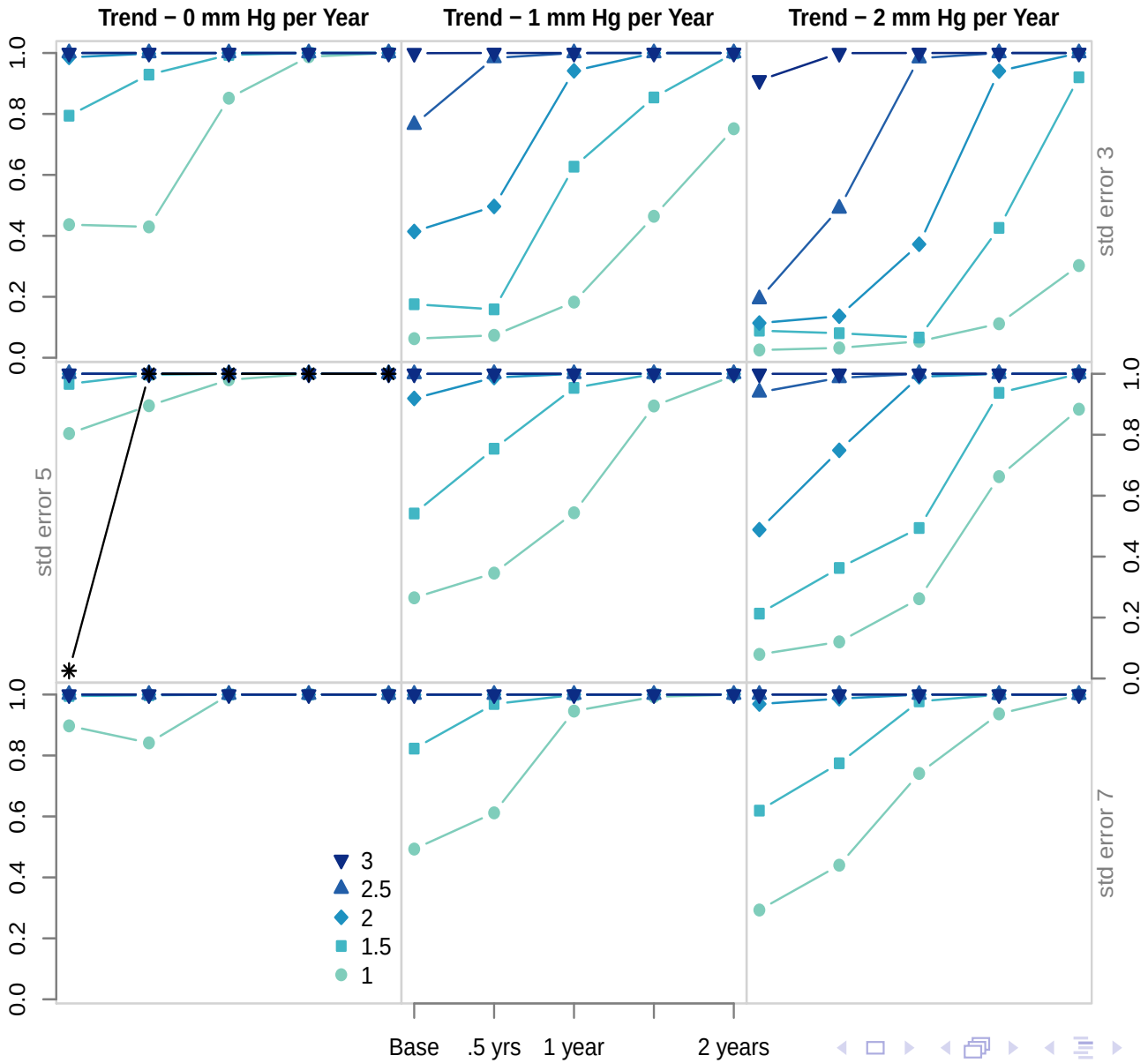
Apparent Treatment Effects Rule 3 Over Measurements 3 Monthly

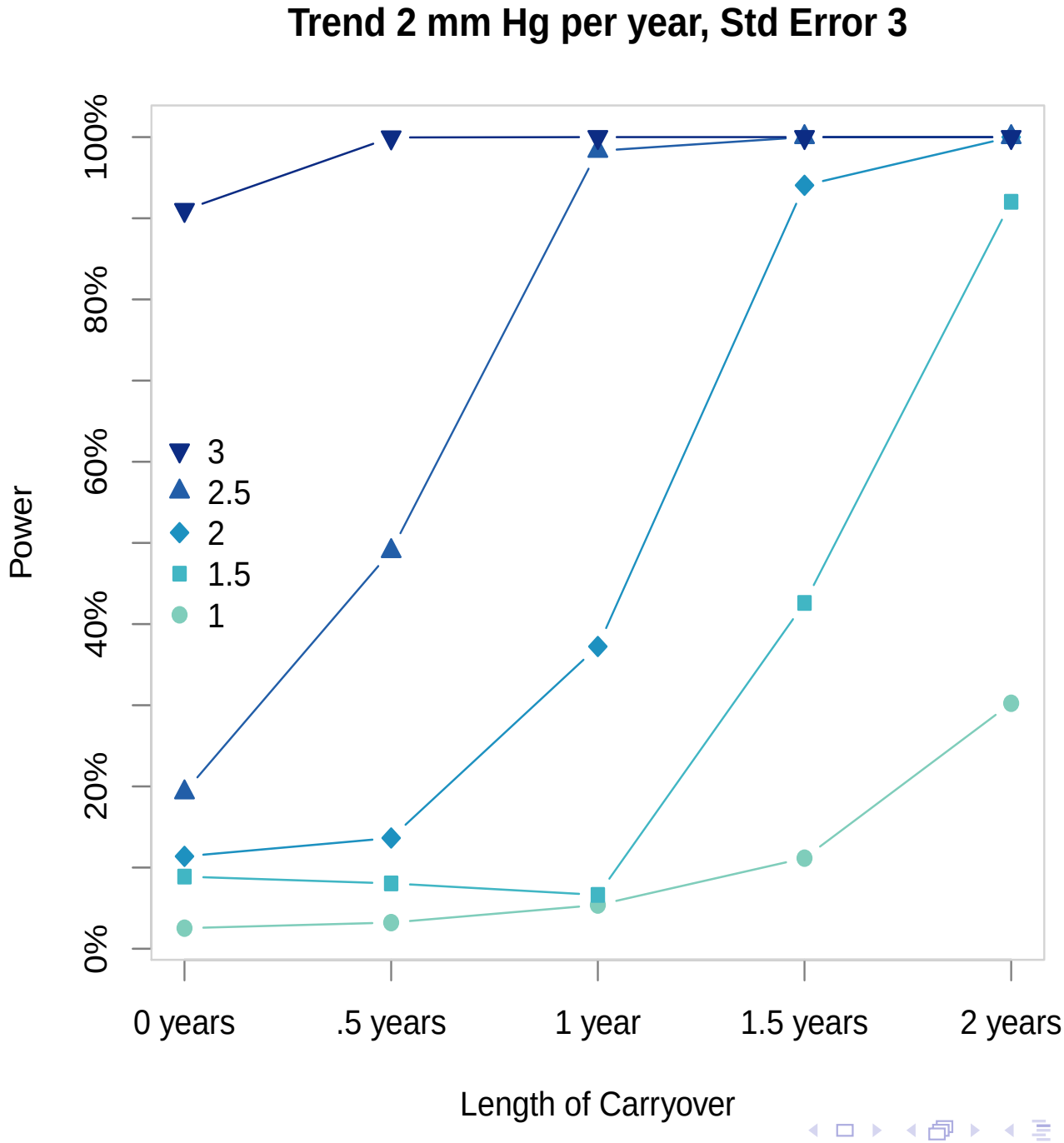


Apparent Treatment Effects − Rule 1 Over Then Check Measurements 3 Monthly



Estimated Powers: Rule 3 Over − Treatment Effect −10 mm Hg, Measurements 3 Monthly




Trend 2 mm Hg per year, Std Error 3
Power
100%
80%
60%
40%
20%
0%
3
2.5
2
1.5
1
0 years
.5 years
1 year
1.5 years
2 years
Length of Carryover

Conclusions

- Varying the start range is ineffective
- Rule 1 Over Then Check - appears to be effective, although easily accessible in the real world as we have no way of finding a person's "treated" BP.
- Cross Over Trial designed Next
- Then more complex stuff - TBA

Acknowledgements

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