# Diagnosing and Accommodating Pandemic Effects on Ongoing Research

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## Some possible pandemic-related impacts on a study

*Under investigator control*

. High-level changes

    Study discontinuation

    Change to aims, population, outcome, design

. Modification of Recruitment Methods

. Modification of Experimental Intervention

    Discontinuation

    Temporary delivery interruption

    Change in modality of delivery (allow for intra-person heterogeneity?)

    Change in fidelity (not always under investigator control)

. Modification of Design Features

    Change in randomization method

    Change in data collection modality/location/frequency/timing/personnel

Some possible pandemic-related impacts on a study

*Not under investigator control*

Secular/contextual factors, e.g.,
- Reduced autonomy of motion
- Changes in normative behavior
- Changes in access to resources
- Economic impacts

. Participant reaction to study modifications and/or pandemic
- Change in recruitment rate/population
- Change in intervention/protocol adherence
- Change in study retention

. Participant experience with pandemic disease
- Participant tests positive for pandemic disease
- Participant treated, hospitalized, and/or dies from pandemic disease

. Other pandemic-related participant factors
- Reduced health care access
- Essential worker status
- Changes in food/housing security, housing composition

Some possible pandemic-related impacts on a study

When pandemic onset occurs mid study, many investigators choose to
- Temporarily halt the study
- Institute design & protocol modifications in response to the pandemic
- Resume the study with modifications

Pandemic-related factors could impact study effect estimates

Document and describe
- Pandemic-related contextual factors
- Study design and protocol modifications
- Participant-level pandemic-related factors hypothesized to impact…
    - Ongoing study participation and intervention adherence
    - Study outcomes
- Useful for sensitivity analyses

## Possible estimates for a study that was ongoing at pandemic onset

### Pooled-data estimates
Use both pre-pandemic and pandemic-era data to estimate effect

Hopefully, the pandemic does not impact study results or
any such impacts can be statistically accommodated

What is possible/reasonable depends on the data & diagnostics

If assumptions underlying a pooled-data estimate are not supported,
or are not testable, then consider one or both of the following

### Pre-pandemic estimate
Use pre-pandemic data to estimate a pre-pandemic effect

### Pandemic-era estimate
Use pandemic-era data to estimate a pandemic-era effect

*Not every study will result in data that can support
pooled-data, pre-pandemic, and pandemic-era estimates*

# Simple Example: Cross-sectional study with 50%-50% recruitment during the pre-pandemic and pandemic-era periods
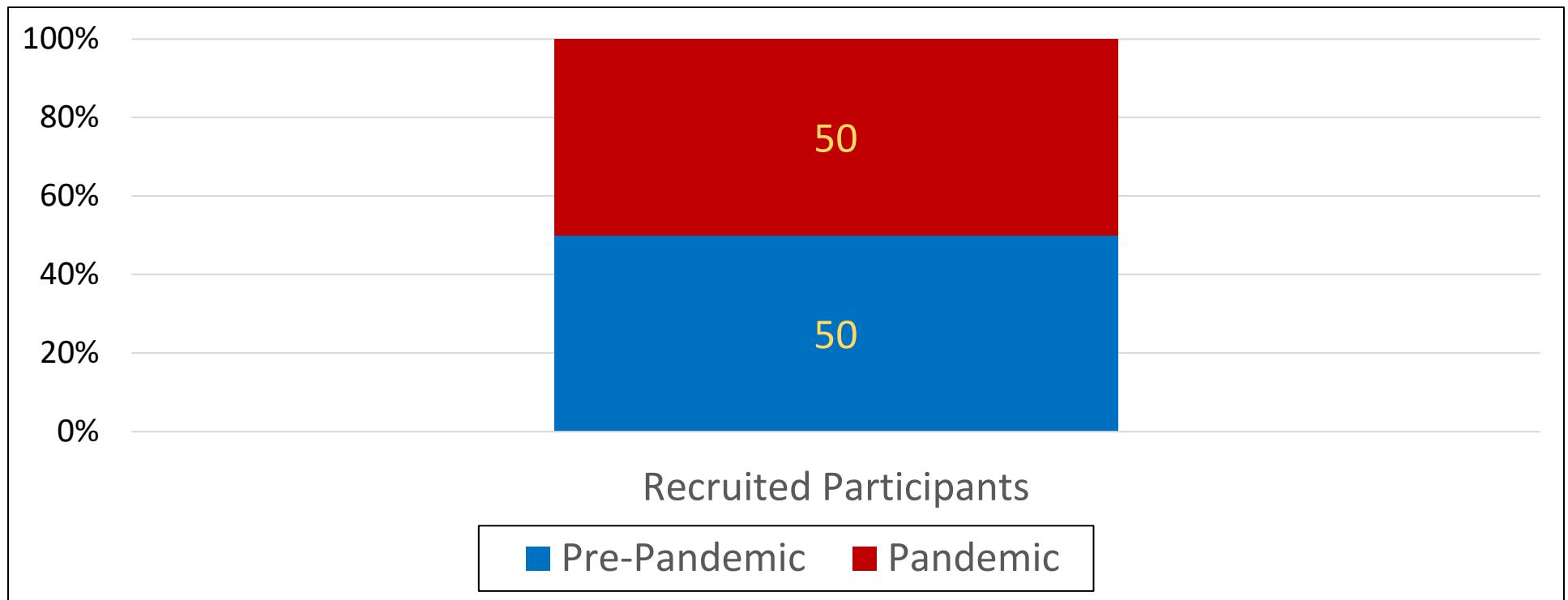


## Example Goal

Estimate the association btw. dating app use (*x*) & unprotected sex (*y*)

. Diagnostic Q: Is the association of *x* and *y* roughly equivalent across the pre-pandemic and pandemic periods?

## Simple Example: Cross-sectional study with 50%-50% recruitment during the pre-pandemic and pandemic periods

### App-by-Pandemic Interaction
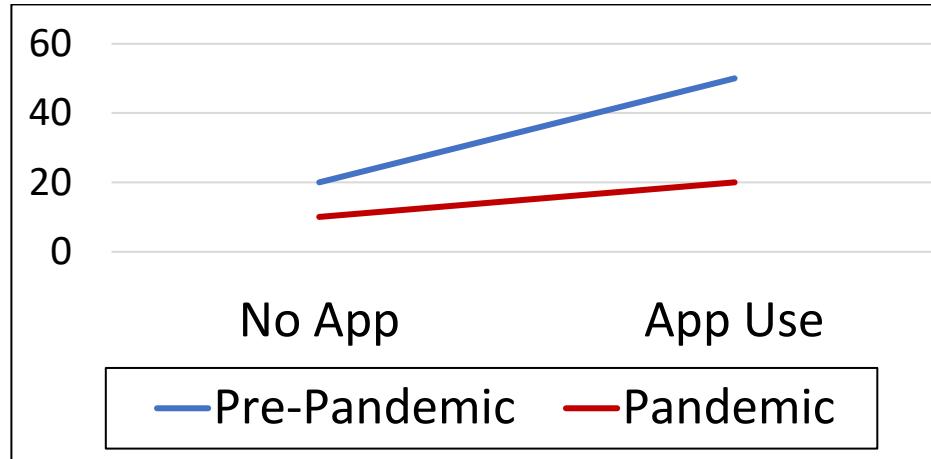


### No Interaction Effect
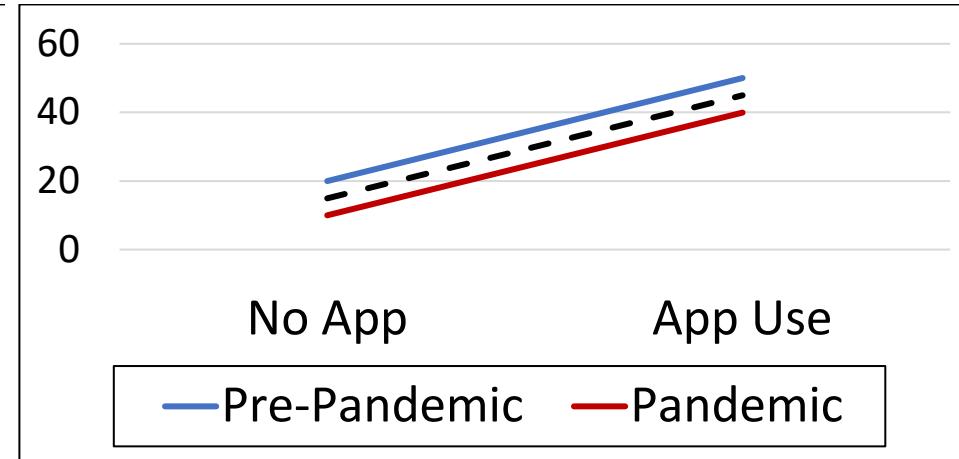


Dx: test effects of app use, pandemic period, & interaction on outcome

If interaction effect is significant, report effects stratified by period
i.e., separate pre-pandemic and pandemic-era estimates
B/c of confounding, unclear reasons for non-equivalent associations

If interaction effect is n.s., report association pooled across periods, conditional on pandemic period indicator.
i.e., the pooled-data estimate (dotted black line)

# Timing of Scheduled Study Visits Relative to Pandemic Onset
## Longitudinal Study Prototype
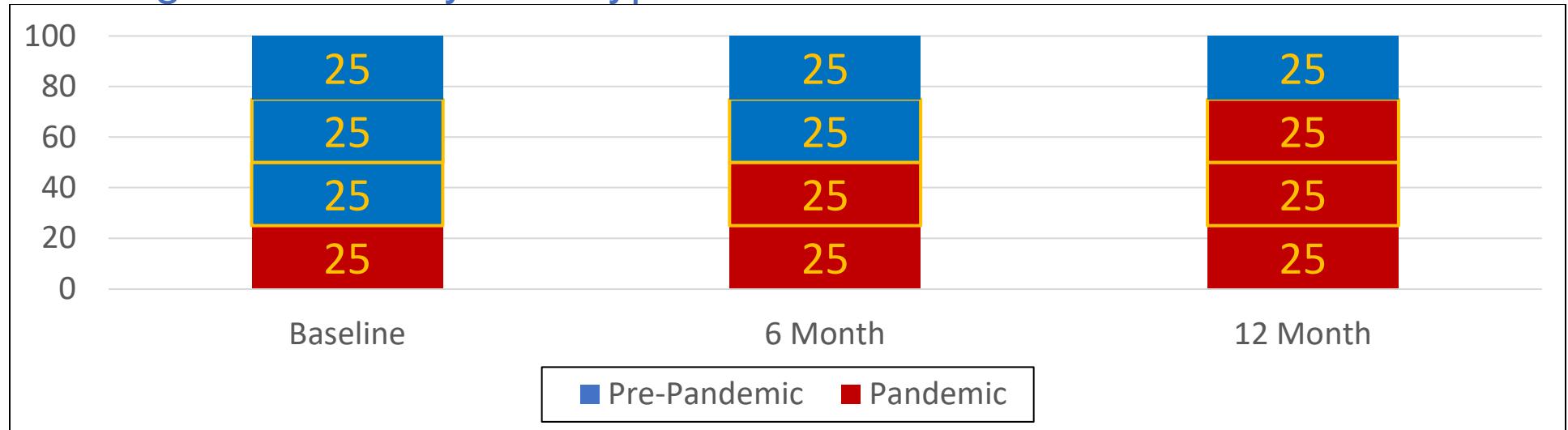


## Possible Estimates

. Pooled-data. Fit model to all data
   Choose when group, time, and/or group*time effect estimates
      are not modified by pandemic status.
   Best power when defensible.

. Pre-pandemic. Fit model to pre-pandemic-only ('blue') data.

. Pandemic-era. Fit model to pandemic-era-only ('red') data.

# Pooled-data Estimate

| | | Baseline | 6 Month | 12 Month |
|---|---|---|---|---|



| Pattern | Pandemic indicator | | |
|---|---|---|---|
| **1** | 0 | 0 | 0 |
| **2** | 1 | 0 | 0 |
| **3** | 1 | 1 | 0 |
| **4** | 1 | 1 | 1 |
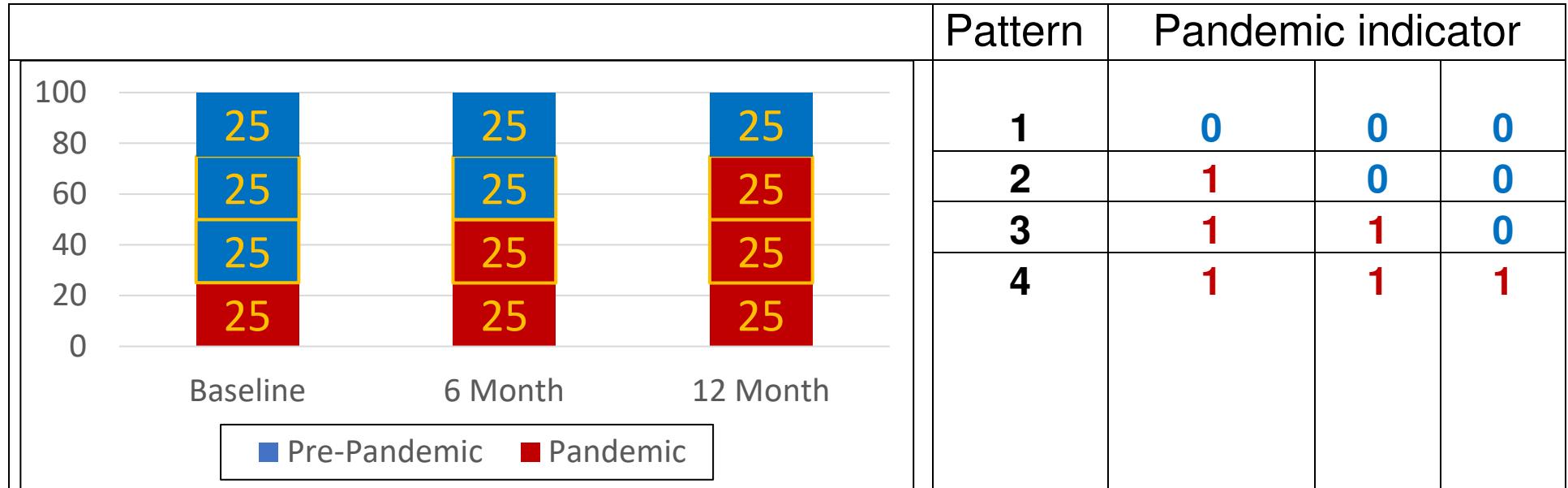
Diagnostic ITT model includes group (G), time (T), & pandemic (P) effects plus G*T, G*P, T*P, and G*T*P interactions, i.e. the saturated model

Backward elimination of non-substantial interaction effects

Impact of pandemic-related interaction effects on pooled-data estimates
 . group*pandemic:       biased pooled-data group main effects
 . time*pandemic:        biased pooled-data time   main effects
 . group*time*pandemic: biased pooled-data group, time, group*time effects

# Simulations

Each simulation…

. Generated a single-replicate large sample: $N$=10K

. Assumed an RCT with 3 fixed assessment times: Base, 6mth, 12mth

. Assumed two pandemic states balanced within each intervention group

. Assumed four sequences of pandemic status across assessment times

| | | | | | Sequence | Pandemic indicator | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1 | 1 | 1 | 1 |
| | | | | | 2 | 0 | 1 | 1 |
| | | | | | 3 | 0 | 0 | 1 |
| | | | | | 4 | 0 | 0 | 0 |

Chart values (Baseline, 6 Month, 12 Month): each bar segment = 25

Legend: Pre-Pandemic, Pandemic
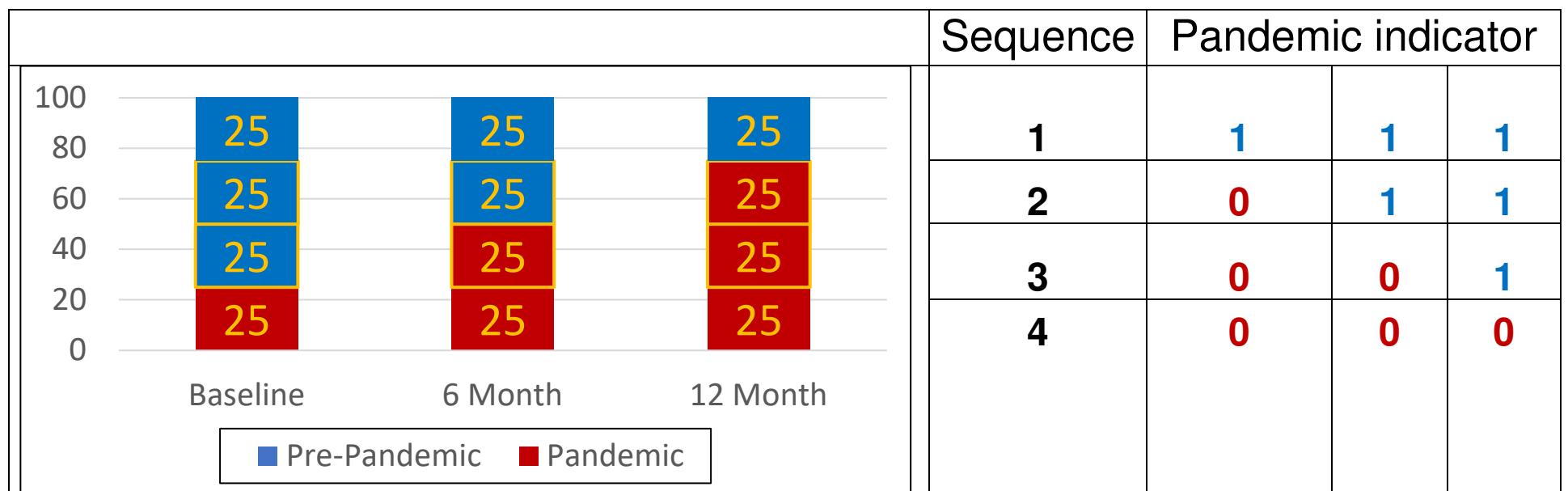
# Simulations

Five data-generating—or population—models (PM)
  All observations independent

PM1. Base Population Model (group, time, group*time, pandemic effects)

$$y_{it} = d_{6m} + d_{12m}*2 + group_i*d_{6m} + group_i*d_{12m}*2 + pandemic_{it} + e_{it},$$

where $d_{6m}$ & $d_{12m}$ are dummies for time; group=0 for Ctl & group=1 for Trt

Pre-Pandemic Population Parameters

|               | Base | 6mth | 12mth | $\Delta_{6-B}$ | $\Delta_{12-6}$ | $\Delta_{12-B}$ |
|---------------|------|------|-------|-------|--------|--------|
| Ctl           | 0    | 1    | 2     | 1     | 1      | 2      |
| Trt           | 0    | 4    | 7     | 4     | 3      | 7      |
| $\Delta_{Trt-Ctl}$ | 0    | 3    | 5     | 3     | 2      | 5      |

. black=population means,  orange=group effects,  blue=time effects,  red=group*time effects

PM1 contains no interactions involving pandemic.

Therefore, we expect that an appropriate data analysis will yield
  unbiased pooled-data group, time, and group*time effect estimates

# Simulations

## Population models

| Pop. Model | Population effects included | E: re. pooled-data estimates | |
|---|---|---|---|
| | | biased | unbiased |
| PM1 (G\|T, P) | group<br>time<br>group*time<br>pandemic | | group<br>time<br>group*time |
| PM2 (G\|T, G\|P) | PM1 +<br>group*pandemic | group | time<br>group*time |
| PM3 (G\|T, T\|P) | PM1 +<br>time*pandemic | time | group<br>group*time |
| PM4 (G\|T\|P@2) | PM1 +<br>group*pandemic<br>time*pandemic | group<br>time | group*time |
| PM5 (G\|T\|P) | PM1 +<br>group*pandemic<br>time*pandemic<br>group*time*pandemic | group<br>time<br>group*time | |

# Simulations

The pre-pandemic expectations are identical for PM1 - PM5

The pandemic-era expectations are unique to each population model

E.g., the expected values for population model 5 (PM5) follow

## PM5 Pre-Pandemic Population Parameters

|  | Base | 6mth | 12mth | $\Delta_{6-B}$ | $\Delta_{12-6}$ | $\Delta_{12-B}$ |
|---|---|---|---|---|---|---|
| Ctl | 0 | 1 | 2 | 1 | 1 | 2 |
| Trt | 0 | 4 | 7 | 4 | 3 | 0 |
| $\Delta_{Trt-Ctl}$ | 0 | 3 | 5 | 3 | 2 | 5 |

## PM5 Pandemic-Era Population Parameters.

|  | Base | 6mth | 12mth | $\Delta_{6-B}$ | $\Delta_{12-6}$ | $\Delta_{12-B}$ |
|---|---|---|---|---|---|---|
| Ctl | -1 | -1 | 1 | 0 | 2 | 2 |
| Trt | -2 | -1 | 5 | 1 | 6 | 7 |
| $\Delta_{Trt-Ctl}$ | -1 | 0 | 4 | 1 | 4 | 5 |

## PM5 Pandemic-era minus Pre-pandemic

|  | Base | 6mth | 12mth | $\Delta_{6-B}$ | $\Delta_{12-6}$ | $\Delta_{12-B}$ |
|---|---|---|---|---|---|---|
| Ctl | -1 | -2 | -1 | -1 | -1 | 0 |
| Trt | -2 | -5 | -2 | -3 | 3 | 7 |
| $\Delta_{Trt-Ctl}$ | -1 | -3 | -1 | -2 | 2 | 0 |

# Simulations: Sequence Sets of Pandemic Status

By selecting from among the 4 pandemic status sequences,
create 6 sets of sequences representing different study designs



S(1,2,3,4)

S(1,2  )
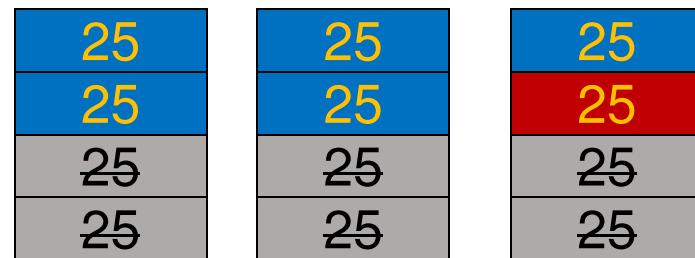
S(1,2,3  )
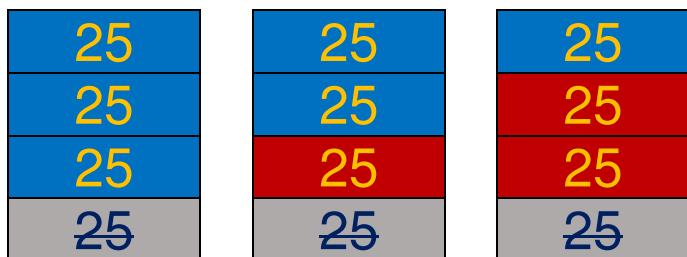
S(  3,4)
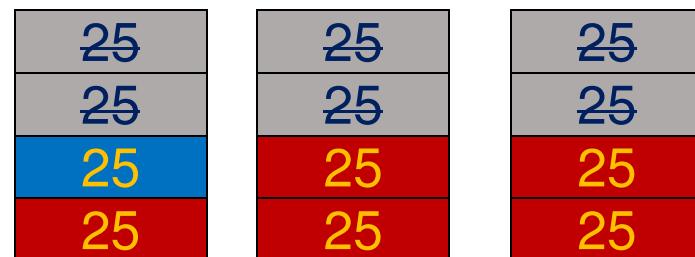
S(  2,3,4)
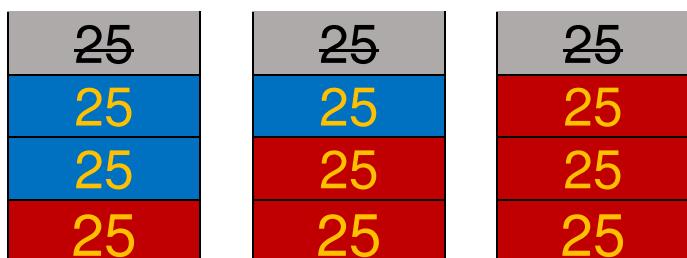
S(  2,3  )
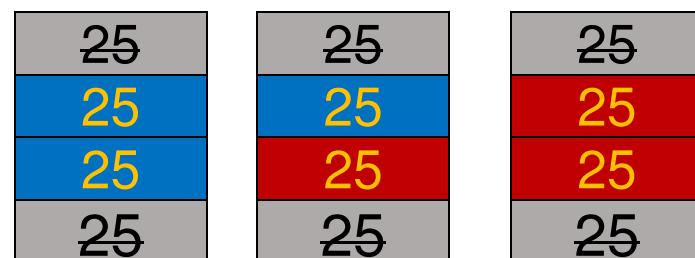
# Simulations

30 simulated conditions: 5 pop. models × 6 pandemic status sequences
   . For S(1,2,3,4), results from all 5 population models are covered
   . For remaining sequences, results from one pop. model are reported

## Additional simulations include

a. A variation of PM5 with 'simpler' T*P and G*T*P effects

b. Possible augmentation of studies w/ S(1,2,3), S(1,2), and S(2,3)
   to include a pandemic-era baseline

S(1,2,3 ) **Augmented**

| 25 | 25 | 25 |
| 25 | 25 | 25 |
| 25 | 25 | 25 |
| **25** | 25 | 25 |

S(1,2   ) **Augmented**

| 25 | 25 | 25 |
| 25 | 25 | 25 |
| **25** | 25 | 25 |
| 25 | 25 | 25 |

S(  2,3  ) **Augmented**

| 25 | 25 | 25 |
| 25 | 25 | 25 |
| 25 | 25 | 25 |
| **25** | 25 | 25 |
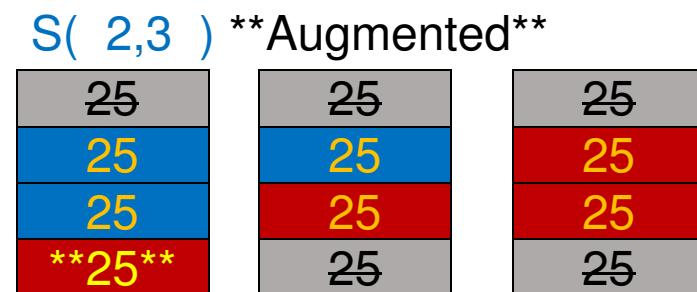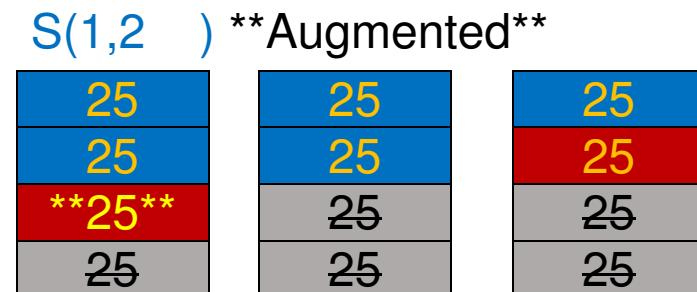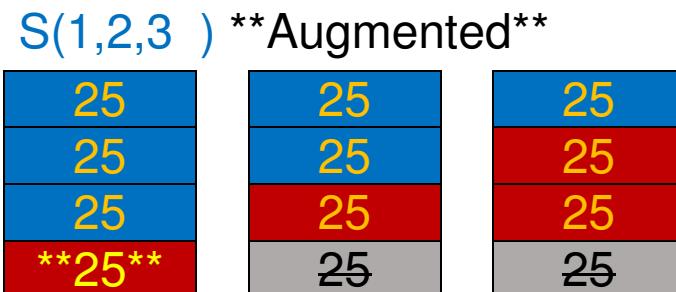
# Four Types of Models Fit to Simulated Data

## 1. Diagnostic (Dx) Model

Start with 3-way interaction model

Backward elimination of non-substantial effects that include pandemic

The final empirical model is the labeled the Analysis Model

For interactions with ≥2df, test the corresponding simple 1df effects

```
proc genmod data=x;
 class Group Time Pandemic;
 model Y = Group|Time|Pandemic / type3;
      estimate '----------------------------------------' int 0;
      estimate ' Dx: Simple 2x2 Effects of Time*Pandemic ' int 0;
      estimate '----------------------------------------' int 0;
      estimate 'Time*Pandemic: Base- 6mth'            Time*Pandemic 1 -1 -1  1  0  0;
      estimate 'Time*Pandemic: 6mth-12mth'            Time*Pandemic 0  0  1 -1 -1  1;
      estimate 'Time*Pandemic: Base-12mth'            Time*Pandemic 1 -1  0  0 -1  1;
      estimate '----------------------------------------' int 0;
      estimate ' Dx: 2x2x2 Effects of Group*Time*Pandemic' int 0;
      estimate '----------------------------------------' int 0;
      estimate 'Group*Time*Pandemic: Base- 6mth'      Group*Time*Pandemic  1 -1 -1  1  0  0
                                                                          -1  1  1 -1  0  0;
      estimate 'Group*Time*Pandemic: 6mth-12mth'      Group*Time*Pandemic  0  0  1 -1 -1  1
                                                                           0  0 -1  1  1 -1;
      estimate 'Group*Time*Pandemic: Base-12mth'      Group*Time*Pandemic  1 -1  0  0 -1  1
                                                                          -1  1  0  0  1 -1;
run;
```

## Four Types of Models Fit to Simulated Data

## 2. ANOVA Model

. Fit the Analysis Model w/ group, time, & pandemic as classification vars

. SAS GLM parameterization of all classification variables is convenient

. Produce 16 custom 1df effect estimates including…

    group main effects at each assessment time                        (×3)

    group main effect averaged across 6 &12 months           (×1)

    2×2 group*time interaction effects, e.g., $G*T_{(base-6m)}$, $G*T_{(base-12m)}$ (×3)

    Simple effects of time w/in each group, e.g., $T_{(base-6m)}$ in Trt grp   (×6)

    Group-averaged effects of time, e.g., $T_{(base-6m)}$ Ctl & Trt average  (×3)

```
proc genmod data=x;
 class Group Time Pandemic;
 model Y = Group|Time <retained Pandemic effects> /type3;
 estimate ' Simple Group Main Effects        ' int 0;
 estimate ' Trt v Ctl @ Base                 ' Group -1 1 Group*Time -1  0  0  1  0  0;
 estimate ' Trt v Ctl @ 6mth                 ' Group -1 1 Group*Time  0 -1  0  0  1  0;
 estimate ' Trt v Ctl @ 12mth                ' Group -1 1 Group*Time  0  0 -1  0  0  1;
 estimate ' Trt v Ctl @ 6mth+12mth: Time-Avg ' Group -1 1 Group*Time  0 -.5 -.5  0 .5 .5;
  <more ESTIMATE statements>;
run;
```

Include Pandemic-related effects
retained in Analysis Model

ESTIMATE statements
produce 16 simple effects.

## Four Types of Models Fit to Simulated Data

3. ANCOVA Model (pooled-data & stratified estimates)
. Fit the Analysis Model w/ group & time as classification vars.

    SAS GLM parameterization of all classification variables is convenient

Model pandemic as a 'continuous' covariate

Estimate each of the 16 simple effects for each pandemic state
    The 16 effects conditioned on pandemic=0 and
    The 16 effects conditioned on pandemic=1

ANOVA model could do this. In SAS, ANCOVA model is much simpler

> Pandemic is a covariate: not in CLASS statement

> Use LSMESTIMATE (not ESTIMATE) statements to calculate the 16 simple effects. One set of 16 for the pre-pandemic estimates and another set for the pandemic-era estimates.

```
proc genmod data=x;
  class Group Time;
   model Y = Group|Time <retained Pandemic effects> / type3;

  lsmestimate Group       'Simple Group Main Effects  ' 0   0                        /at Pandemic=0;
  lsmestimate Group*Time 'Trt v Ctl @  Base, PrePand ' -1   0    0  1  0   0 /at Pandemic=0;
  lsmestimate Group*Time 'Trt v Ctl @  6Mth, PrePand '  0  -1    0  0  1   0 /at Pandemic=0;
  lsmestimate Group*Time 'Trt v Ctl @ 12Mth, PrePand '  0   0   -1  0  0   1 /at Pandemic=0;
  lsmestimate Group*Time 'Trt v Ctl @ 6+12mth, PrePand'  0 -.5 -.5  0 .5  .5 /at Pandemic=0;
  …
  lsmestimate group*time 'Trt v Ctl @  Base, PandEra  ' -1   0    0  1  0   0 /at Pandemic=1 ;
  <more LSMESTIMATE statements>;
run;
```

# Four Types of Models Fit to Simulated Data

## 4. Stratified Models

. Fit pandemic-stratified models w/ group, time, & group*time effects (G|T)
   I.e., one model fit to pre-pandemic data & one fit to pandemic-era data.

   SAS GLM parameterization of all classification variables is convenient

Try to estimate each of the 16 simple effects for each pandemic state

Stratified models are 'safe harbors' but are often result in fewer estimates
   that can be (relatively) inefficient

```
proc genmod data=x;
  class Group Time;
  model Y = Group|Time / type3;
  where Pandemic=0;
```

For the pre-pandemic stratified model,
   restrict to pre-pandemic data.

Fit a second stratified model to pandemic-era data

ESTIMATE statements produce
16 simple effects.

Note that. e.g., Group*Time will
not be fully represented for some
combinations of sequence pattern
and pandemic status.

```
estimate ' Simple Group Main Effects          ' int 0;
estimate ' Trt v Ctl @ Base                    ' Group -1 1 Group*Time -1   0   0  1  0  0;
estimate ' Trt v Ctl @ 6mth                    ' Group -1 1 Group*Time  0  -1   0  0  1  0;
estimate ' Trt v Ctl @ 12mth                   ' Group -1 1 Group*Time  0   0  -1  0  0  1;
estimate ' Trt v Ctl @ 6mth+12mth: Time-Avg ' Group -1 1 Group*Time  0 -.5 -.5  0 .5 .5;
    <more ESTIMATE statements>;

run;
```

# Summaries of Simulation Results

. In many (most?) cases, ANCOVA is equal to or better than ANOVA

. Stratified analyses are a last resort but also have some Dx function

. Mostly, I present ANCOVA and Stratified estimates side by side

. I present ANOVA results within limited contexts

. For <u>jointly unbiased</u> estimates, I also present the relative efficiency (RE)
    of ANCOVA versus Stratified estimates

. If no RE is reported, then estimate is biased, or bias is indeterminable


RE is estimated by comparing corresponding standard error estimates
    across two competing models, e.g., ANCOVA vs. Stratified

$$\widehat{RE}_{\text{ANCOVA:Strat}} = \hat{\sigma}^2_{\text{Strat}}/\hat{\sigma}^2_{\text{ANCOVA}},$$

RE can be considered a ratio of effective sample sizes,
    e.g., an RE of 2.0 suggests that a Stratified analysis would require
    a doubling of sample size to obtain efficiency equivalent to
    the original ANCOVA model

## Simulations with S(1,2,3,4)

The first simulations consider analysis of data with S(1234)

group will be fully crossed with pandemic for all sequence sets
    i.e., each pandemic state is observed within each group

However, in many studies time will not be fully crossed with pandemic.
    We first consider simulations where time & pandemic are
        fully crossed, i.e., S(1,2,3,4)

## S(1,2,3,4) simulated sample sizes by sequence

| Sequence | Base | 6mth | 12mth |
|---|---|---|---|
| 1 | 2500 | 2500 | 2500 |
| 2 | 2500 | 2500 | 2500 |
| 3 | 2500 | 2500 | 2500 |
| 4 | 2500 | 2500 | 2500 |

## S(1,2,3,4) simulated sample sizes by pandemic

| pandemic | Base | 6mth | 12mth |
|---|---|---|---|
| 0 | 7500 | 5000 | 2500 |
| 1 | 2500 | 5000 | 7500 |

Scenario 01: PM1 [G|T, P], S(1,2,3,4)

Diagnostic (Dx) model tested up to 3-way interaction.

| Source | df | χ2 | p |
|---|---|---|---|
| group | 1 | 5465.15 | <.0001 |
| time | 2 | 22381.4 | <.0001 |
| group*time | 2 | 3479.57 | <.0001 |
| pandemic | 1 | 5734.55 | <.0001 |
| group*pandemic | 1 | 0.01 | 0.9214 |
| time*pandemic | 2 | 0.26 | 0.8803 |
| group*time*pandemic | 2 | 1.21 | 0.5458 |

Via backward elimination, drop non-substantial pandemic-related effects

In this case, the G*P, T*P, and G*T*P effects are dropped

The final empirical model is labeled as the Analysis Model, here G|T, P

Prognosis
. No G*T*P effect: Expect unbiased pooled-data group*time  effects
. No G*P or G*T*P effect: Expect unbiased pooled-data group effects
. No T*P or G*T*P effect: Expect unbiased pooled-data time effects

Scenario 01: PM1 [G|T, P], S(1,2,3,4)

Diagnostic model (Dx). A closer look.

Note that the time effect has 3 categories and 2df

So, the time*pandemic and group*time*pandemic effects have 2df

For Type3 tests w/ ≥2df, construct corresponding 1df tests

```
                                         Estimate        se          p
  Dx: Simple 2x2 Effects of Time*Pandemic      .          .          .
--------------------------------------        .          .          .
 Time*Pandemic: Base- 6mth              -0.0141      0.0306     0.6444
 Time*Pandemic: 6mth-12mth               0.0117      0.0306     0.7018
 Time*Pandemic: Base-12mth              -0.0024      0.0327     0.9413
 --------------------------------------       .          .          .
                                              .          .          .
  Dx: 2x2x2 Effects of Group*Time*Pandemic    .          .          .
--------------------------------------        .          .          .
 Group*Time*Pandemic: Base- 6mth         0.0643      0.0612     0.2930
 Group*Time*Pandemic: 6mth-12mth        -0.0097      0.0612     0.8744
 Group*Time*Pandemic: Base-12mth         0.0547      0.0654     0.4032
 --------------------------------------       .          .          .
```

No surprises in this case because the Type3 test statistics were tiny.
   Even so, this is an important part of the Dx model

# Scenario 01: PM1 [G|T, P], S(1,2,3,4)

```
                                                PANDEMIC=0                 PANDEMIC=1
                                            b      se      RE        b_      se      RE
Simple Group Main Effects
Trt v Ctl @ Base                 : E=0,0   0.01   0.020   1.32     0.01   0.020   4.02
Trt v Ctl @ 6mth                 : E=3,3   2.95   0.020   1.98     2.95   0.020   2.01
Trt v Ctl @ 12mth                : E=5,5   4.99   0.020   3.97     4.99   0.020   1.34
Trt v Ctl @ 6mth+12mth: Time-Avg: E=4,4   3.97   0.014   2.97     3.97   0.014   1.67
-----------------------------------------

Group*Time Interaction Effects
2x2 Int: Trt v Ctl @Base- 6m     : E=3,3   2.94   0.028   1.65     2.94   0.028   3.02
2x2 Int: Trt v Ctl @  6m-12m     : E=2,2   2.04   0.028   2.97     2.04   0.028   1.67
2x2 Int: Trt v Ctl @Base-12m     : E=5,5   4.98   0.028   2.64     4.98   0.028   2.68
-----------------------------------------

Within-Group Time Main Effects
Ctl:  6mth v Base                : E=1,1   1.03   0.020   1.61     1.03   0.020   2.94
Ctl: 12mth v 6mth                : E=1,1   0.95   0.020   2.90     0.95   0.020   1.63
Ctl: 12mth v Base                : E=2,2   1.98   0.021   2.40     1.98   0.021   2.44

Trt:  6mth v Base                : E=4,4   3.97   0.020   1.61     3.97   0.020   2.94
Trt: 12mth v 6mth                : E=3,3   2.99   0.020   2.90     2.99   0.020   1.63
Trt: 12mth v Base                : E=7,7   6.97   0.021   2.40     6.97   0.022   2.44
-----------------------------------------

Group-Averaged Time Main Effects
Group-Avg:  6mth v Base          : E=2.5,2.5  2.50  0.014  1.57    2.50   0.014   2.87
Group-Avg: 12mth v 6mth          : E=2.0,2.0  1.97  0.014  2.83    1.97   0.014   1.59
Group-Avg: 12mth v Base          : E=4.5,4.5  4.48  0.015  2.20    4.48   0.015   2.23
-----------------------------------------
Note. E= holds expected values for pre-pandemic and pandemic-era, respectively
```

As expected, estimates equivalent and unbiased across pandemic states.

ANCOVA had a RE advantage versus Stratified analyses

# Scenario 02: PM2 [G|T, G|P], S(1,2,3,4)

| | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
| | | b | se | RE | b_ | se | RE |
| **Simple Group Main Effects** | | | | | | | |
| Trt v Ctl @ Base | : E=0,−1 | 0.01 | 0.021 | 1.20 | −0.99 | 0.027 | 2.11 |
| Trt v Ctl @ 6mth | : E=3, 2 | 2.95 | 0.023 | 1.41 | 1.94 | 0.023 | 1.43 |
| Trt v Ctl @ 12mth | : E=5, 4 | 4.99 | 0.027 | 2.09 | 3.99 | 0.021 | 1.22 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4, 3 | | 3.97 | 0.021 | 1.32 | 2.97 | 0.017 | 1.15 |
| ---------------------------------------- | | | | | | | |
| **Group*Time Interaction Effects** | | | | | | | |
| 2x2 Int: Trt v Ctl @Base− 6m | : E=3,3 | 2.94 | 0.029 | 1.57 | 2.94 | 0.029 | 2.87 |
| 2x2 Int: Trt v Ctl @ 6m−12m | : E=2,2 | 2.04 | 0.029 | 2.83 | 2.04 | 0.029 | 1.59 |
| 2x2 Int: Trt v Ctl @Base−12m | : E=5,5 | 4.99 | 0.031 | 2.20 | 4.99 | 0.031 | 2.23 |
| ---------------------------------------- | | | | | | | |
| **Within-Group Time Main Effects** | | | | | | | |
| Ctl: 6mth v Base | : E=1,1 | 1.03 | 0.020 | 1.57 | 1.03 | 0.020 | 2.87 |
| Ctl: 12mth v 6mth | : E=1,1 | 0.95 | 0.020 | 2.83 | 0.95 | 0.020 | 1.59 |
| Ctl: 12mth v Base | : E=2,2 | 1.98 | 0.021 | 2.20 | 1.98 | 0.021 | 2.23 |
| | | | | | | | |
| Trt: 6mth v Base | : E=4,4 | 3.97 | 0.020 | 1.57 | 3.97 | 0.020 | 2.87 |
| Trt: 12mth v 6mth | : E=3,3 | 2.99 | 0.020 | 2.83 | 2.99 | 0.020 | 1.59 |
| Trt: 12mth v Base | : E=7,7 | 6.97 | 0.021 | 2.20 | 6.97 | 0.021 | 2.23 |
| ---------------------------------------- | | | | | | | |
| **Group-Averaged Time Main Effects** | | | | | | | |
| Group-Avg: 6mth v Base | : E=2.5,2.5 | 2.50 | 0.014 | 1.57 | 2.50 | 0.014 | 2.87 |
| Group-Avg: 12mth v 6mth | : E=2.0,2.0 | 1.97 | 0.014 | 2.83 | 1.97 | 0.014 | 1.59 |
| Group-Avg: 12mth v Base | : E=4.5,4.5 | 4.48 | 0.015 | 2.20 | 4.48 | 0.015 | 2.23 |
| ---------------------------------------- | | | | | | | |

Note. E= holds expected values for pre-pandemic and pandemic-era periods, respectively

- As expected, estimates equivalent except for group main effects

- All estimates unbiased

- RE advantage of ANCOVA

- ANCOVA a hybrid model: both pooled-data and 'stratified' estimates

# Scenario 02: PM2 [G|T, G|P], S(1,2,3,4)

## New focus: ANOVA vs ANCOVA Pre-Pandemic Estimates

PANDMEIC=0

| | | ANOVA | | | ANCOVA | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | b | se | RE | b | se | RE |
| **Simple Group Main Effects** | | | | | | | |
| Trt v Ctl @ Base | : E=0,-1 | -0.49 | 0.021 | . | 0.008 | 0.021 | 1.20 |
| Trt v Ctl @ 6mth | : E=3, 2 | 2.45 | 0.020 | . | 2.95 | 0.023 | 1.41 |
| Trt v Ctl @ 12mth | : E=5, 4 | 4.49 | 0.021 | . | 4.99 | 0.027 | 2.09 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4, 3 | | 3.47 | 0.014 | . | 3.97 | 0.021 | 1.32 |
| ------------------------------------------ | | | | | | | |
| **Group*Time Interaction Effects** | | | | | | | |
| 2x2 Int: Trt v Ctl @Base- 6m | : E=3,3 | 2.94 | 0.029 | 1.57 | 2.94 | 0.029 | 1.57 |
| 2x2 Int: Trt v Ctl @ 6m-12m | : E=2,2 | 2.04 | 0.029 | 2.83 | 2.04 | 0.029 | 2.83 |
| 2x2 Int: Trt v Ctl @Base-12m | : E=5,5 | 4.99 | 0.031 | 2.20 | 4.99 | 0.031 | 2.20 |
| ------------------------------------------ | | | | | | | |
| **Within-Group Time Main Effects** | | | | | | | |
| Ctl: 6mth v Base | : E=1,1 | 1.03 | 0.020 | 1.57 | 1.03 | 0.020 | 1.57 |
| Ctl: 12mth v 6mth | : E=1,1 | 0.95 | 0.020 | 2.83 | 0.95 | 0.020 | 2.83 |
| Ctl: 12mth v Base | : E=2,2 | 1.98 | 0.021 | 2.20 | 1.98 | 0.021 | 2.20 |
| | | | | | | | |
| Trt: 6mth v Base | : E=4,4 | 3.97 | 0.020 | 1.57 | 3.97 | 0.020 | 1.57 |
| Trt: 12mth v 6mth | : E=3,3 | 2.99 | 0.020 | 2.83 | 2.99 | 0.020 | 2.83 |
| Trt: 12mth v Base | : E=7,7 | 6.97 | 0.021 | 2.20 | 6.97 | 0.021 | 2.20 |
| ------------------------------------------ | | | | | | | |
| **Group-Averaged Time Main Effects** | | | | | | | |
| Group-Avg: 6mth v Base | : E=2.5,2.5 | 2.50 | 0.014 | 1.57 | 2.50 | 0.014 | 1.57 |
| Group-Avg: 12mth v 6mth | : E=2.0,2.0 | 1.97 | 0.014 | 2.83 | 1.97 | 0.014 | 2.83 |
| Group-Avg: 12mth v Base | : E=4.5,4.5 | 4.48 | 0.015 | 2.20 | 4.48 | 0.015 | 2.20 |

ANOVA group main effects are averaged across pandemic status.

Again, ANOVA could obtain the same results as ANCOVA.
   ANCOVA approach is a lot easier within SAS.

# Scenario 03: PM3 [G|T, T|P], S(1,2,3,4)

## Refocus on comparing ANCOVA versus Stratified model estimates

| | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
| | | b | se | RE | b_ | se | RE |
| **Simple Group Main Effects** | | | | | | | |
| Trt v Ctl @ Base | : E=0,0 | 0.01 | 0.020 | 1.32 | 0.01 | 0.020 | 4.02 |
| Trt v Ctl @ 6mth | : E=3,3 | 2.95 | 0.020 | 1.98 | 2.95 | 0.020 | 2.01 |
| Trt v Ctl @ 12mth | : E=5,5 | 4.99 | 0.020 | 3.97 | 4.99 | 0.020 | 1.34 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4,4 | | 3.97 | 0.014 | 2.97 | 3.97 | 0.014 | 1.67 |
| ----------------------------------------- | | | | | | | |
| **Group*Time Interaction Effects** | | | | | | | |
| 2x2 Int: Trt v Ctl @Base- 6m | : E=3,3 | 2.94 | 0.028 | 1.65 | 2.94 | 0.028 | 3.02 |
| 2x2 Int: Trt v Ctl @ 6m-12m | : E=2,2 | 2.04 | 0.028 | 2.97 | 2.04 | 0.028 | 1.67 |
| 2x2 Int: Trt v Ctl @Base-12m | : E=5,5 | 4.98 | 0.028 | 2.64 | 4.98 | 0.028 | 2.68 |
| ----------------------------------------- | | | | | | | |
| **Within-Group Time Main Effects** | | | | | | | |
| Ctl:  6mth v Base | : E=1,0 | 1.03 | 0.023 | 1.24 | 0.02 | 0.028 | 1.51 |
| Ctl: 12mth v 6mth | : E=1,0 | 0.94 | 0.028 | 1.48 | −0.04 | 0.023 | 1.25 |
| Ctl: 12mth v Base | : E=2,0 | 1.98 | 0.027 | 1.44 | −0.01 | 0.027 | 1.46 |
| | | | | | | | |
| Trt:  6mth v Base | : E=4,3 | 3.98 | 0.023 | 1.24 | 2.97 | 0.028 | 1.51 |
| Trt: 12mth v 6mth | : E=3,2 | 2.99 | 0.028 | 1.48 | 2.00 | 0.023 | 1.25 |
| Trt: 12mth v Base | : E=7,5 | 6.97 | 0.027 | 1.44 | 4.97 | 0.027 | 1.46 |
| ----------------------------------------- | | | | | | | |
| **Group-Averaged Time Main Effects** | | | | | | | |
| Group-Avg:  6mth v Base | : E=2.5,1.5 | 2.51 | 0.018 | 0.99 | 1.49 | 0.024 | 1.00 |
| Group-Avg: 12mth v 6mth | : E=2.0,1.0 | 1.97 | 0.024 | 0.99 | 0.98 | 0.018 | 1.00 |
| Group-Avg: 12mth v Base | : E=4.5,2.5 | 4.48 | 0.023 | 0.99 | 2.48 | 0.023 | 1.00 |

. All estimates unbiased

. As expected, G and G*T effects equivalent across pandemic status

. ANCOVA RE gains except for group-averaged time effects.

# Scenario 04: PM4 [G|T|P@2], S(1,2,3,4)

| | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
| | | b | se | RE | b_ | se | RE |
| **Simple Group Main Effects** | | | | | | | |
| Trt v Ctl @ Base | : E=0,-1 | 0.01 | 0.021 | 1.203 | -0.99 | 0.027 | 2.119 |
| Trt v Ctl @ 6mth | : E=3, 2 | 2.95 | 0.023 | 1.418 | 1.94 | 0.023 | 1.438 |
| Trt v Ctl @ 12mth | : E=5, 4 | 4.99 | 0.027 | 2.090 | 3.99 | 0.021 | 1.220 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4, 3 | | 3.97 | 0.021 | 1.323 | 2.97 | 0.017 | 1.157 |
| ---------------------------------------- | | | | | | | |
| **Group*Time Interaction Effects** | | | | | | | |
| 2x2 Int: Trt v Ctl @Base- 6m | : E=3,3 | 2.94 | 0.029 | 1.576 | 2.94 | 0.029 | 2.877 |
| 2x2 Int: Trt v Ctl @  6m-12m | : E=2,2 | 2.04 | 0.029 | 2.837 | 2.04 | 0.029 | 1.598 |
| 2x2 Int: Trt v Ctl @Base-12m | : E=5,5 | 4.99 | 0.031 | 2.206 | 4.99 | 0.031 | 2.237 |
| ---------------------------------------- | | | | | | | |
| **Within-Group Time Main Effects** | | | | | | | |
| Ctl:  6mth v Base | : E=1,0 | 1.03 | 0.023 | 1.218 | 0.02 | 0.028 | 1.491 |
| Ctl: 12mth v 6mth | : E=1,0 | 0.94 | 0.028 | 1.471 | -0.04 | 0.023 | 1.235 |
| Ctl: 12mth v Base | : E=2,0 | 1.98 | 0.027 | 1.369 | -0.01 | 0.027 | 1.388 |
| | | | | | | | |
| Trt:  6mth v Base | : E=4,3 | 3.98 | 0.023 | 1.218 | 2.97 | 0.028 | 1.491 |
| Trt: 12mth v 6mth | : E=3,2 | 2.99 | 0.028 | 1.471 | 2.00 | 0.023 | 1.235 |
| Trt: 12mth v Base | : E=7,5 | 6.97 | 0.027 | 1.369 | 4.97 | 0.027 | 1.388 |
| ---------------------------------------- | | | | | | | |
| **Group-Averaged Time Main Effects** | | | | | | | |
| Group-Avg:  6mth v Base | : E=2.5,1.5 | 2.51 | 0.018 | 0.992 | 1.49 | 0.024 | 1.006 |
| Group-Avg: 12mth v 6mth | : E=2.0,1.0 | 1.97 | 0.024 | 0.992 | 0.98 | 0.018 | 1.006 |
| Group-Avg: 12mth v Base | : E=4.5,2.5 | 4.48 | 0.023 | 0.992 | 2.48 | 0.023 | 1.006 |

. All estimates unbiased

. As expected, G*T effects equivalent across pandemic status

. RE gains except for group-averaged time effects.

# Scenario 05: PM5 [G|T|P], S(1,2,3,4)

| | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
| | | b | se | RE | b_ | se | RE |
| **Simple Group Main Effects** | | | | | | | |
| Trt v Ctl @ Base | : E=0,−1 | −0.00 | 0.023 | 0.993 | −0.96 | 0.040 | 1.007 |
| Trt v Ctl @ 6mth | : E=3, 0 | 2.96 | 0.028 | 0.993 | −0.06 | 0.028 | 1.007 |
| Trt v Ctl @ 12mth | : E=5, 1 | 5.00 | 0.040 | 0.993 | 0.99 | 0.023 | 1.007 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4,0.5 | | 3.98 | 0.024 | 0.993 | 0.46 | 0.018 | 1.007 |
| ---------------------------------- | | | | | | | |
| **Group*Time Interaction Effects** | | | | | | | |
| 2x2 Int: Trt v Ctl @Base− 6m | : E=3,1 | 2.96 | 0.036 | 0.993 | 0.90 | 0.049 | 1.007 |
| 2x2 Int: Trt v Ctl @  6m−12m | : E=2,1 | 2.04 | 0.049 | 0.993 | 1.05 | 0.036 | 1.007 |
| 2x2 Int: Trt v Ctl @Base−12m | : E=5,2 | 5.01 | 0.046 | 0.993 | 1.95 | 0.046 | 1.007 |
| ---------------------------------- | | | | | | | |
| **Within−Group Time Main Effects** | | | | | | | |
| Ctl:  6mth v Base | : E=1,0 | 1.02 | 0.025 | 0.993 | 0.04 | 0.034 | 1.007 |
| Ctl: 12mth v 6mth | : E=1,0 | 0.94 | 0.034 | 0.993 | −0.04 | 0.025 | 1.007 |
| Ctl: 12mth v Base | : E=2,0 | 1.97 | 0.032 | 0.993 | 0.00 | 0.032 | 1.007 |
| | | | | | | | |
| Trt:  6mth v Base | : E=4,1 | 3.99 | 0.025 | 0.993 | 0.94 | 0.034 | 1.007 |
| Trt: 12mth v 6mth | : E=3,1 | 2.99 | 0.034 | 0.993 | 1.00 | 0.025 | 1.007 |
| Trt: 12mth v Base | : E=7,2 | 6.98 | 0.032 | 0.993 | 1.95 | 0.032 | 1.007 |
| ---------------------------------- | | | | | | | |
| **Group−Averaged Time Main Effects** | | | | | | | |
| Group-Avg:  6mth v Base | : E=2.5,0.5 | 2.51 | 0.018 | 0.993 | 0.49 | 0.024 | 1.007 |
| Group-Avg: 12mth v 6mth | : E=2.0,0.5 | 1.97 | 0.024 | 0.993 | 0.48 | 0.018 | 1.007 |
| Group-Avg: 12mth v Base | : E=4.5,1.0 | 4.48 | 0.023 | 0.993 | 0.98 | 0.023 | 1.007 |

. All estimates unbiased, but are specific to pandemic status

. As expected no equivalent effects across pandemic status

. No RE gains. ANCOVA effectively a Stratified analysis

# A case where the ANOVA setup outperforms the ANCOVA setup

## PM5 Dx model results

```
Source                              df        χ2              p       .
 Group                              1      10714.2          <.0001
 Time                               2      28030.5          <.0001
 Group*Time                         2      11415.7          <.0001
 Pandemic                           1      67394.5          <.0001
 Group*Pandemic                     1      10907.0          <.0001
 Time*Pandemic                      2      11579.7          <.0001
 Group*Time*Pandemic                2       2290.30         <.0001


                                        Estimate      StdErr           p
 Dx: Simple 2x2 Effects of Time*Pandemic
 Time*Pandemic: Base- 6mth               -2.0141      0.0306       <.0001
 Time*Pandemic: Base-12mth               -3.5024      0.0327       <.0001
 ---------------------------------------     .           .            .
 Dx: 2x2x2 Effects of Group*Time*Pandemic
 Group*Time*Pandemic: Base- 6mth          2.0643      0.0612       <.0001
 Group*Time*Pandemic: Base-12mth          3.0547      0.0654       <.0001
 ---------------------------------------     .           .            .
```

For PM5, the T*P and the G*T*P effects each result in two substantial contrasts.

For T*P, pandemic status modifies change from Base-6m & from Base-12m

For G*T*P, pandemic status modifies the G*T effect from Base-6m & Base-12m

What if the population model G*T*P effect was less complicated?

# Scenario 05c: PM5c [G|T|P]c, S(1,2,3,4)

PM5c includes T*P and G*T*P interaction effects whereby pandemic significantly

 ( i) modifies the time effect from Base-6m, but not the effect from Base-12m

(ii) modifies the G*T effect from Base-6m, but not the effect from Base-12m

## PM5c Dx model results

```
Source                          DF        χ2                p      .
Group                            1     20345.0          <.0001
Time                             2     78385.1          <.0001
Group*Time                       2     23707.8          <.0001
Pandemic                         1     28327.8          <.0001
Group*Pandemic                   1     4265.38          <.0001
Time*Pandemic                    2     6065.11          <.0001
Group*Time*Pandemic              2     1553.47          <.0001


                                         Estimate      StdErr          p      .
 Dx: Simple Effects of Time*Pandemic
 Time*Pandemic: Base- 6mth                -2.0141      0.0306     <.0001
 Time*Pandemic: Base-12mth                -0.0024      0.0327      0.9413
 ----------------------------------------
 Dx: 2x2 Effects of Group*Time*Pandemic
 Group*Time*Pandemic: Base- 6mth           2.0643      0.0612     <.0001
 Group*Time*Pandemic: Base-12mth           0.0547      0.0654      0.4032
```

Recall that PM5 is the worst-case population model.

What happens when the nature of the PM5 G*T*P effect is simplified?

ANOVA setup versus ANCOVA setup

```
                                              ANOVA                ANCOVA(pre-pandemic)
                                          b      se      RE        b      se      RE   .
Simple Group Main Effects                 .      .       .                        .
Trt v Ctl @ Base            : E=0,-1    -0.48  0.023     .       -0.00  0.023    0.99
Trt v Ctl @ 6mth            : E=3, 0     1.45  0.020     .        2.96  0.028    0.99
Trt v Ctl @ 12mth           : E=5, 4     4.50  0.023     .        5.00  0.040    0.99
Trt v Ctl @ 6mth+12mth: Time-Avg: E=4, 2 2.97  0.015     .        3.98  0.024    0.99
-----------------------------------------
Group*Time Interaction Effects
2x2 Int: Trt v Ctl @Base- 6m : E=3,1     1.93  0.030     .        2.96  0.036    0.99
2x2 Int: Trt v Ctl @  6m-12m : E=2,4     3.04  0.030     .        2.04  0.049    0.99
2x2 Int: Trt v Ctl @Base-12m : E=5,5     4.98  0.032    1.98      5.01  0.046    0.99
-----------------------------------------
Within-Group Time Main Effects
Ctl:  6mth v Base           : E=1,0      0.53  0.021     .        1.02  0.025    0.99
Ctl: 12mth v 6mth           : E=1,2      1.45  0.021     .        0.94  0.034    0.99
Ctl: 12mth v Base           : E=2,2      1.98  0.023    1.98      1.97  0.032    0.99

Trt:  6mth v Base           : E=4,1      2.47  0.021     .        3.99  0.025    0.99
Trt: 12mth v 6mth           : E=3,6      4.50  0.021     .        2.99  0.034    0.99
Trt: 12mth v Base           : E=7,7      6.97  0.023    1.98      6.98  0.032    0.99
-----------------------------------------
Group-Averaged Time Main Effects
Group-Avg:  6mth v Base     : E=2.5,0.5  1.50  0.015     .        2.51  0.018    0.99
Group-Avg: 12mth v 6mth     : E=2.0,4.0  2.97  0.015     .        1.97  0.024    0.99
Group-Avg: 12mth v Base     : E=4.5,4.5  4.48  0.016    1.98      4.48  0.023    0.99
-----------------------------------------
```

In this case, ANOVA produces mostly pandemic-averaged results. However, under PM5c, for all T(Base-12m) and G*T(Base-12m) effects, the ANOVA setup obtains a RE gain of 2.0 versus the ANCOVA setup

## Simulations with S(1,2,3)

The 2$^{nd}$ set of simulations consider analyses of data with S(1,2,3)
    where time & pandemic are not fully crossed

S(1,2,3) simulated sample sizes by sequence

| Sequence | Base | 6mth | 12mth |
|---|---|---|---|
| 1 | 2500 | 2500 | 2500 |
| 2 | 2500 | 2500 | 2500 |
| 3 | 2500 | 2500 | 2500 |

S(1,2,3) simulated sample sizes by pandemic

| Pandemic | Base | 6mth | 12mth |
|---|---|---|---|
| 0 | 7500 | 2500 | 5000 |
| 1 | . | 5000 | 2500 |

In short, the data do not include a pandemic-era baseline

Simulations with S(1,2,3)

With S(1,2,3) [and S(2,3,4)] the Dx model tests of the time*pandemic
    and group*time*pandemic effects will each have 1df. Still testable.

Results Summary
. All ANCOVA estimates were unbiased within each population model:
    PM1 through PM5.

. However, T*P or G*T*P effects in the population model made it
    impossible to estimate pandemic-era time effects beyond $\Delta_{6m-12m}$

. If you have S(1,2,3) and want a full set of pandemic-era estimates,
    then consider augmenting the study to add a pandemic-era baseline

. ANCOVA offered efficiency gains, except for PM5.

# Scenario 06: PM3 [G|T, T|P], S(1,2,3)

|  | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
|  | | b | se | RE | b_ | se | RE |
| **Simple Group Main Effects** | | | | | | | |
| Trt v Ctl @ Base | : E=0,0 | −0.00 | 0.023 | 0.99 | −0.00 | . | . |
| Trt v Ctl @ 6mth | : E=3,3 | 2.97 | 0.023 | 1.48 | 2.97 | −0.021 | 3.04 |
| Trt v Ctl @ 12mth | : E=5,5 | 4.99 | 0.023 | 2.97 | 4.99 | 0.005 | 1.52 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4,4 | | 3.98 | 0.016 | 2.23 | 3.98 | −0.007 | 2.28 |
| ---------------------------------------- | | | | | | | |
| **Group*Time Interaction Effects** | | | | | | | |
| 2x2 Int: Trt v Ctl @Base- 6m | : E=3,3 | 2.97 | 0.032 | 1.24 | 2.97 | . | . |
| 2x2 Int: Trt v Ctl @   6m-12m | : E=2,2 | 2.02 | 0.032 | 2.23 | 2.02 | 0.027 | 2.28 |
| 2x2 Int: Trt v Ctl @Base-12m | : E=5,5 | 5.00 | 0.032 | 1.98 | 5.00 | . | . |
| ---------------------------------------- | | | | | | | |
| **Within-Group Time Main Effects** | | | | | | | |
| Ctl:  6mth v Base | : E=1,0 | 1.02 | 0.024 | 1.10 | . | . | . |
| Ctl: 12mth v 6mth | : E=1,0 | 0.95 | 0.029 | 1.37 | −0.015 | −0.013 | 1.40 |
| Ctl: 12mth v Base | : E=2,0 | 1.98 | 0.028 | 1.32 | . | . | . |
|  | | | | | | | |
| Trt:  6mth v Base | : E=4,3 | | | | . | . | . |
| Trt: 12mth v 6mth | : E=3,2 | 2.98 | 0.029 | 1.37 | 2.00 | 0.013 | 1.40 |
| Trt: 12mth v Base | : E=7,5 | 6.98 | 0.028 | 1.32 | . | . | . |
| ---------------------------------------- | | | | | | | |
| **Group-Averaged Time Main Effects** | | | | | | | |
| Group-Avg:  6mth v Base | : E=2.5,1.5 | 2.51 | 0.018 | 0.99 | . | . | . |
| Group-Avg: 12mth v 6mth | : E=2.0,1.0 | 1.97 | 0.024 | 0.99 | 0.99 | −0.000 | 1.01 |
| Group-Avg: 12mth v Base | : E=4.5,2.5 | 4.48 | 0.023 | 0.99 | . | . | . |
| ---------------------------------------- | | | | | | | |

. All estimates unbiased

. As expected G and G*T effects are equivalent across pandemic status

. RE gains of ANCOVA, except for time-averaged group effects

. For a full set of pandemic-era estimates, add a pandemic-era baseline

. Comment: ANCOVA produced all pandemic-era G and G*T estimates

## Simulations with S(2,3,4)

The 3rd set of simulations considered analysis of data with S(2,3,4) where, again, time & pandemic are not fully crossed

S(2,3,4) simulated sample sizes by sequence

| Sequence | Base | 6mth | 12mth |
|----------|------|------|-------|
| 2 | 2500 | 2500 | 2500 |
| 3 | 2500 | 2500 | 2500 |
| 4 | 2500 | 2500 | 2500 |

S(2,3,4) simulated sample sizes by pandemic

| pandemic | Base | 6mth | 12mth |
|----------|------|------|-------|
| 0 | 5000 | 2500 | . |
| 1 | 2500 | 5000 | 7500 |

Results Summary. Similar to S(1,2,3) except for two main points

. If the Analysis model includes T*P or G*T*P effects,
    then you will not obtain a full set of pre-pandemic estimates.

. An augmented design would require a pre-pandemic 12m assessment,
    but often that won't be possible.

Simulations with S(1,2)

The 4th set of simulations considered analysis of data with S(1,2) where, again, time & pandemic are not fully crossed

S(1,2) simulated sample sizes by sequence

| Sequence | Base | 6mth | 12mth |
|---|---|---|---|
| 1 | 2500 | 2500 | 2500 |
| 2 | 2500 | 2500 | 2500 |

S(1,2,3) simulated sample sizes by pandemic

| Pandemic | Base | 6mth | 12mth |
|---|---|---|---|
| 0 | 5000 | 5000 | 2500 |
| 1 | . | . | 2500 |

With S(1,2), the Dx model cannot test T*P or G*T*P effects.
    Under S(1,2), those effects have 0 df

Even so, if the pop. model includes G*T*P effects (PM5), then S(1,2) can result in some biased ANCOVA effects.

We consider PM5, S(1,2) to see the worst case.

## Scenario 07: PM5 [G|T|P], S(1,2)

| | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
| | | b | se | RE | b | se | RE |
| **Simple Group Main Effects** | | | | . | | | . |
| Trt v Ctl @ Base | : E=0,−1 | 0.02 | 0.028 | 1.00 | −3.97 | 0.062 | . |
| Trt v Ctl @ 6mth | : E=3, 0 | 2.96 | 0.028 | 1.00 | −1.03 | 0.062 | . |
| Trt v Ctl @ 12mth | : E=5, 1 | 5.00 | 0.039 | 1.00 | 1.01 | 0.039 | 1.01 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4,0.5 | | 3.98 | 0.024 | 1.00 | −0.01 | 0.046 | . |
| **Group*Time Interaction Effects** | | | | . | | | . |
| 2x2 Int: Trt v Ctl @Base- 6m | : E=3,1 | 2.94 | 0.039 | 1.00 | 2.94 | 0.039 | . |
| 2x2 Int: Trt v Ctl @  6m-12m | : E=2,1 | 2.04 | 0.048 | 1.00 | 2.04 | 0.048 | . |
| 2x2 Int: Trt v Ctl @Base-12m | : E=5,2 | 4.98 | 0.048 | 1.00 | 4.98 | 0.048 | . |
| **Within-Group Time Main Effects** | | | | . | | | . |
| Ctl:  6mth v Base | : E=1,0 | 1.04 | 0.028 | 1.00 | 1.04 | 0.028 | . |
| Ctl: 12mth v 6mth | : E=1,0 | 0.94 | 0.034 | 1.00 | 0.94 | 0.034 | . |
| Ctl: 12mth v Base | : E=2,0 | 1.99 | 0.034 | 1.00 | 1.99 | 0.034 | . |
| | | | | . | | | . |
| Trt:  6mth v Base | : E=4,1 | 3.98 | 0.028 | 1.00 | 3.98 | 0.028 | . |
| Trt: 12mth v 6mth | : E=3,1 | 2.99 | 0.034 | 1.00 | 2.99 | 0.034 | . |
| Trt: 12mth v Base | : E=7,2 | 6.98 | 0.034 | 1.00 | 6.98 | 0.034 | . |
| **Group-Averaged Time Main Effects** | | | | . | | | . |
| Group-Avg:  6mth v Base | : E=2.5,0.5 | 2.51 | 0.019 | 1.00 | 2.51 | 0.019 | . |
| Group-Avg: 12mth v 6mth | : E=2.0,0.5 | 1.97 | 0.024 | 1.00 | 1.97 | 0.024 | . |
| Group-Avg: 12mth v Base | : E=4.5,1.0 | 4.48 | 0.024 | 1.00 | 4.48 | 0.024 | . |

Unbiased pre-pandemic effects; essentially a stratified analysis with PM5

Biased pandemic-era group main effects, except group at 12 months

Pandemic-era G*T and time estimates are really pre-pandemic estimates,
   but no way to know that: can't test T*P or G*T*P in Dx model w/ S(1,2)

Augmenting S(1,2) w/ pandemic-era baseline would allow testing
      a pandemic-era G*T$_{(Base-12m)}$ effect.

# Scenario 07: PM5 [G|T|P], S(1,2)

| | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
| | | b | se | RE | b | se | RE |
| **Simple Group Main Effects** | | | | . | | | . |
| Trt v Ctl @ Base | : E=0,-1 | 0.02 | 0.028 | 1.00 | -3.97 | 0.062 | . |
| Trt v Ctl @ 6mth | : E=3, 0 | 2.96 | 0.028 | 1.00 | -1.03 | 0.062 | . |
| Trt v Ctl @ 12mth | : E=5, 1 | 5.00 | 0.039 | 1.00 | 1.01 | 0.039 | 1.01 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4,0.5 | | 3.98 | 0.024 | 1.00 | -0.01 | 0.046 | . |
| **Group*Time Interaction Effects** | | | | . | | | . |
| 2x2 Int: Trt v Ctl @Base- 6m | : E=3,1 | 2.94 | 0.039 | 1.00 | 2.94 | 0.039 | . |
| 2x2 Int: Trt v Ctl @ 6m-12m | : E=2,1 | 2.04 | 0.048 | 1.00 | 2.04 | 0.048 | . |
| 2x2 Int: Trt v Ctl @Base-12m | : E=5,2 | 4.98 | 0.048 | 1.00 | 4.98 | 0.048 | . |
| **Within-Group Time Main Effects** | | | | . | | | . |
| Ctl:  6mth v Base | : E=1,0 | 1.04 | 0.028 | 1.00 | 1.04 | 0.028 | . |
| Ctl: 12mth v 6mth | : E=1,0 | 0.94 | 0.034 | 1.00 | 0.94 | 0.034 | . |
| Ctl: 12mth v Base | : E=2,0 | 1.99 | 0.034 | 1.00 | 1.99 | 0.034 | . |
| | | | | . | | | . |
| Trt:  6mth v Base | : E=4,1 | 3.98 | 0.028 | 1.00 | 3.98 | 0.028 | . |
| Trt: 12mth v 6mth | : E=3,1 | 2.99 | 0.034 | 1.00 | 2.99 | 0.034 | . |
| Trt: 12mth v Base | : E=7,2 | 6.98 | 0.034 | 1.00 | 6.98 | 0.034 | . |
| **Group-Averaged Time Main Effects** | | | | . | | | . |
| Group-Avg:  6mth v Base | : E=2.5,0.5 | 2.51 | 0.019 | 1.00 | 2.51 | 0.019 | . |
| Group-Avg: 12mth v 6mth | : E=2.0,0.5 | 1.97 | 0.024 | 1.00 | 1.97 | 0.024 | . |
| Group-Avg: 12mth v Base | : E=4.5,1.0 | 4.48 | 0.024 | 1.00 | 4.48 | 0.024 | . |

Note. **RE** only shown if ANCOVA effect is equivalent to the corresponding Stratified effect

Conservative S(1,2). Only report ANCOVA effects that are equivalent to corresponding Stratified estimates, i.e., here that includes
   . All pre-pandemic estimates (green)
   . Pandemic-era estimate of 12-month group effect (purple)
   . Nothing else

ANCOVA S(1,2) will have RE gains if G*P effect not in the pop. model

## Simulations with S(3,4)

The 5th set of simulations considered analysis of data with S(3,4) where, again, time & pandemic are not fully crossed

S(3,4) simulated sample sizes by sequence

| Sequence | Base | 6mth | 12mth |
|---|---|---|---|
| 3 | 2500 | 2500 | 2500 |
| 4 | 2500 | 2500 | 2500 |

S(3,4) simulated sample sizes by pandemic

| pandemic | Base | 6mth | 12mth |
|---|---|---|---|
| 0 | 2500 | . | . |
| 1 | 2500 | 5000 | 5000 |

Results Summary. Similar to S(1,2) except for two main points

. If the pop. model includes T*P or G*T*P effects,
   then you will not obtain all unbiased pre-pandemic estimates.

. An augmented design would require a pre-pandemic 6m and/or 12m
   assessments, but often those won't be possible.

## Simulations with S(2,3)

The 6th set of simulations considered analysis of data with S(2,3) where, again, time & pandemic are not fully crossed

S(2,3) simulated sample sizes by sequence

| Sequence | Base | 6mth | 12mth |
|----------|------|------|-------|
| 2 | 2500 | 2500 | 2500 |
| 3 | 2500 | 2500 | 2500 |

S(2,3,4) simulated sample sizes by pandemic

| pandemic | Base | 6mth | 12mth |
|----------|------|------|-------|
| 0 | 5000 | 2500 | . |
| 1 | . | 2500 | 5000 |

Combined with PM5, S(2,3) is the absolute worst case considered.

The baseline to 12m comparison is completely confounded with pandemic status.

# Scenario 08: PM5 [G|T|P], S(2,3)

| | | PANDEMIC=0 | | | PANDEMIC=1 | | |
|---|---|---|---|---|---|---|---|
| | | b | se | RE | b | se | RE |
| **Simple Group Main Effects** | | | | | | | |
| Trt v Ctl @ Base | : E=0,−1 | −0.01 | 0.028 | 1.00 | −2.98 | 0.063 | . |
| Trt v Ctl @ 6mth | : E=3, 0 | 2.96 | 0.040 | 1.00 | −0.00 | 0.040 | 1.00 |
| Trt v Ctl @ 12mth | : E=5, 1 | 3.96 | 0.063 | | 0.99 | 0.028 | 1.00 |
| Trt v Ctl @ 6mth+12mth: Time-Avg: E=4,0.5 | | 3.46 | 0.047 | | 0.49 | 0.024 | 1.00 |
| **Group*Time Interaction Effects** | | | | | | | |
| 2x2 Int: Trt v Ctl @Base− 6m | : E=3,1 | 2.98 | 0.049 | 1.00 | 2.98 | 0.049 | . |
| 2x2 Int: Trt v Ctl @ 6m−12m | : E=2,1 | 0.99 | 0.049 | | 0.99 | 0.049 | 1.00 |
| 2x2 Int: Trt v Ctl @Base−12m | : E=5,2 | 3.97 | 0.069 | | 3.97 | 0.069 | . |
| **Within-Group Time Main Effects** | | | | | | | |
| Ctl:  6mth v Base | : E=1,0 | 1.00 | 0.034 | 1.00 | 1.00 | 0.034 | . |
| Ctl: 12mth v 6mth | : E=1,0 | −0.001 | 0.034 | | −0.00 | 0.034 | 1.00 |
| Ctl: 12mth v Base | : E=2,0 | 0.99 | 0.049 | | 0.99 | 0.049 | . |
| | | | | | | | |
| Trt:  6mth v Base | : E=4,1 | 3.98 | 0.034 | 1.00 | 3.98 | 0.034 | . |
| Trt: 12mth v 6mth | : E=3,1 | 0.99 | 0.034 | | 0.99 | 0.034 | 1.00 |
| Trt: 12mth v Base | : E=7,2 | 4.97 | 0.049 | | 4.97 | 0.049 | . |
| **Group-Averaged Time Main Effects** | | | | | | | |
| Group-Avg:  6mth v Base | : E=2.5,0.5 | 2.49 | 0.024 | 1.00 | 2.49 | 0.024 | . |
| Group-Avg: 12mth v 6mth | : E=2.0,0.5 | 0.49 | 0.024 | | 0.49 | 0.024 | 1.00 |
| Group-Avg: 12mth v Base | : E=4.5,1.0 | 2.98 | 0.034 | | 2.98 | 0.034 | . |

Unbiased pre-pandemic effects for outcomes at Base and 6mth (green)

Unbiased pandemic-era effects for outcomes at 6 and 12 mth (purple)

For S(2,3) ANCOVA has some efficiency gains if there are no G*P effects

Consider augmenting S(2,3) w/ pandemic-era baseline to obtain…
  . A full set of pandemic-era estimates
  . ANCOVA RE gains for population models PM1, PM2, PM3 & PM4

## Final Summary

The ANCOVA setup offers a convenient hybrid approach that produces both pooled-data and stratified estimates, as appropriate.

With 2 groups, 2 pandemic states and >2 assessment times, if…

. Dx model finds no P main or interaction effects. AN(C)OVA: Y=[G|T]

. Dx model finds P effects, but no interactions w/ P. AN(C)OVA: Y=[G|T, P]

. Dx model finds G|P effects, but no T|P or G|T|P. ANCOVA: Y=[G|T, G|P]

. Dx model finds T|P or G|T|P effects. ANCOVA: Y=[Analysis Model]

   If any 1df effects of T|P or G|T|P are non-substantial, then
      additionally estimate 1df interaction effects as in ANOVA setup

Compare effect estimates across Stratified & ANOVA/ANCOVA.
   Some diagnostic value especially with sparse sequence sets

## Final Summary

Plan ahead for best/worst case scenarios wrt modeling options/power.
   Consider conducting simulations with inputs from study data, e.g.,
      . types and prevalence of anticipated pandemic sequences
      . intra-person correlation of repeated assessments

Consult your statistician

# SAS Code

```
*----------------------------------------------------------------------------*;
* _Diagnostic Model_
*
* . GROUP=0 for Ctl, GROUP=1 for Trt
* . TIME=0 for Baseline, TIME=1 for 6months, TIME=2 for 12 Months
* . PANDEMIC=0 for pre-pandemic, PANDEMIC=1 for pandemic-era
*----------------------------------------------------------------------------*;
  proc genmod data=<your data>;
   class GROUP TIME PANDEMIC;
   model Y = GROUP|TIME|PANDEMIC/type3;

* ADD THE FOLLOWING FOR S(1,2,3,4);
      estimate ' Dx: Simple 2x2 Effects of Time*Pandemic ' int 0;
      estimate '------------------------------------' int 0;
      estimate 'Time*Pandemic: Base- 6mth'            TIME*PANDEMIC 1 -1 -1  1  0  0;
      estimate 'Time*Pandemic: 6mth-12mth'            TIME*PANDEMIC 0  0  1 -1 -1  1;
      estimate 'Time*Pandemic: Base-12mth'            TIME*PANDEMIC 1 -1  0  0 -1  1;
      estimate '------------------------------------' int 0;
      estimate ' Dx: 2x2x2 Effects of Group*Time*Pandemic' int 0;
      estimate '------------------------------------' int 0;
      estimate 'Group*Time*Pandemic: Base- 6mth'      GROUP*TIME*PANDEMIC  1 -1 -1  1  0  0   -1  1  1 -1  0  0 ;
      estimate 'Group*Time*Pandemic: 6mth-12mth'      GROUP*TIME*PANDEMIC  0  0  1 -1 -1  1    0  0 -1  1  1 -1;
      estimate 'Group*Time*Pandemic: Base-12mth'      GROUP*TIME*PANDEMIC  1 -1  0  0 -1  1   -1  1  0  0  1 -1;


* ADD THE FOLLOWING FOR S(1,2,3);
      estimate ' Dx: Simple Effects of Time*Pandemic     ' int 0;
      estimate '------------------------------------' int 0;
      estimate 'Time*Pandemic: 6mth-12mth'            TIME*PANDEMIC 0 1 -1 -1  1;
      estimate '------------------------------------' int 0;
      estimate ' Dx: 2x2 Effects of Group*Time*Pandemic  ' int 0;
      estimate '------------------------------------' int 0;
      estimate 'Group*Time*Pandemic: 6mth-12mth'      GROUP*TIME*PANDEMIC 0  1 -1 -1  1    0  -1  1 1 -1;

* ADD THE FOLLOWING FOR S(2,3,4);
      estimate ' Dx: Simple Effects of Time*Pandemic     ' int 0;
      estimate '------------------------------------' int 0;
      estimate 'Time*Pandemic: Base-6mth              ' TIME*PANDEMIC 1 -1 -1  1 0;
      estimate '------------------------------------' int 0;
      estimate ' Dx: 2x2 Effects of Group*Time*Pandemic  ' int 0;
      estimate '------------------------------------' int 0;
      estimate 'Group*Time*Pandemic: Base-6mth         ' GROUP*TIME*PANDEMIC 1 -1 -1  1 0   -1  1 1 -1 0;
      estimate '------------------------------------' int 0;
run;
*----------------------------------------------------------------------------*;
```

```
*--------------------------------------------------------------------------------*;
* _ANOVA Model_
*
* . GROUP=0 for Ctl, GROUP=1 for Trt
* . TIME=0 for Baseline, TIME=1 for 6months, TIME=2 for 12 Months
* . PANDEMIC=0 for pre-pandemic, PANDEMIC=1 for pandemic-era
* . <analysis model> is the empirical model selected via diagnostic modeling.
*--------------------------------------------------------------------------------*;
proc genmod data=<your data>;
   class GROUP TIME PANDEMIC;
    model Y = <analysis model> /type3;

   estimate 'Group Main Effects                     ' int 0;
   estimate " Trt v Ctl @ Base                      " GROUP -1 1 GROUP*TIME -1   0   0  1  0  0;
   estimate " Trt v Ctl @ 6mth                      " GROUP -1 1 GROUP*TIME  0  -1   0  0  1  0;
   estimate " Trt v Ctl @ 12mth                     " GROUP -1 1 GROUP*TIME  0   0  -1  0  0  1;
   estimate " Trt v Ctl @ 6mth+12mth: Time-Avg      " GROUP -1 1 GROUP*TIME  0 -.5 -.5  0 .5 .5;
   estimate ' -------------------------------------' int 0;
   estimate 'Group*Time Interaction Effects         ' int 0;
   estimate '-------------------------------------' int 0;
   estimate " 2x2 Int: Trt v Ctl @Base- 6m          " GROUP*TIME 1 -1  0 -1  1 0;
   estimate " 2x2 Int: Trt v Ctl @  6m-12m          " GROUP*TIME 0  1 -1  0 -1 1;
   estimate " 2x2 Int: Trt v Ctl @Base-12m          " GROUP*TIME 1  0 -1 -1  0 1;
   estimate '-------------------------------------' int 0;
   estimate ' Within-Group Time Main Effects        ' int 0;
   estimate ' -------------------------------------' int 0;
   estimate " Ctl:  6mth v Base                     " TIME -1  1 0 GROUP*TIME -1  1 0  0  0 0;
   estimate " Ctl: 12mth v 6mth                     " TIME  0 -1 1 GROUP*TIME  0 -1 1  0  0 0;
   estimate " Ctl: 12mth v Base                     " TIME -1  0 1 GROUP*TIME -1  0 1  0  0 0;
   estimate '                                       ' int 0;
   estimate " Trt:  6mth v Base                     " TIME -1  1 0 GROUP*TIME  0  0 0 -1  1 0;
   estimate " Trt: 12mth v 6mth                     " TIME  0 -1 1 GROUP*TIME  0  0 0  0 -1 1;
   estimate " Trt: 12mth v Base                     " TIME -1  0 1 GROUP*TIME  0  0 0 -1  0 1;
   estimate ' -------------------------------------' int 0;
   estimate ' Group-Averaged Time Main Effects      ' int 0;
   estimate ' -------------------------------------' int 0;
   estimate " Group-Avg:  6mth v Base               " TIME -1  1 0;
   estimate " Group-Avg: 12mth v 6mth               " TIME  0 -1 1;
   estimate " Group-Avg: 12mth v Base               " TIME -1  0 1;
   estimate ' -------------------------------------' int 0;
  run;
```

```
*-----------------------------------------------------------------------------*;
* _ANCOVA Model_
*
* . GROUP=0 for Ctl, GROUP=1 for Trt
* . TIME=0 for Baseline, TIME=1 for 6months, TIME=2 for 12 Months
* . PANDEMIC=0 for pre-pandemic, PANDEMIC=1 for pandemic-era.
*    For the ANCOVA setup, PANDEMIC is not included in the CLASS statement;
* . <analysis model> is the empirical model selected via diagnostic modeling.
*-----------------------------------------------------------------------------*;
  proc genmod data=<your data>;
  class GROUP TIME;
   model Y = <analysis model> /type3;

  lsmestimate GROUP        '* Pre-Pandemic Estimates *                ' 0 0;
  lsmestimate GROUP        '------------------------------------------' 0 0;
  lsmestimate GROUP        ' Simple Group Main Effects                ' 0 0;
  lsmestimate GROUP*TIME ' Trt v Ctl @  Base,   PrePand              ' -1    0    0   1   0  0 /at PANDEMIC=0 ;
  lsmestimate GROUP*TIME ' Trt v Ctl @  6Mth,   PrePand              '  0   -1    0   0   1  0 /at PANDEMIC=0 ;
  lsmestimate GROUP*TIME ' Trt v Ctl @ 12Mth,   PrePand              '  0    0   -1   0   0  1 /at PANDEMIC=0 ;
  lsmestimate GROUP*TIME ' Trt v Ctl @ 6+12mth, PrePand              '  0  -.5 -.5   0  .5 .5 /at PANDEMIC=0 ;
  lsmestimate GROUP        ' ----------------------------------------' 0  0;
  lsmestimate GROUP        'Group*Time Interaction Effects            ' 0  0;
  lsmestimate GROUP*TIME '2x2 Int: Trt v Ctl @Base- 6m, PrePand     '  1   -1    0  -1   1  0 /at PANDEMIC=0;
  lsmestimate GROUP*TIME '2x2 Int: Trt v Ctl @  6m-12m, PrePand     '  0    1   -1   0  -1  1 /at PANDEMIC=0;
  lsmestimate GROUP*TIME '2x2 Int: Trt v Ctl @Base-12m, PrePand     '  1    0   -1  -1   0  1 /at PANDEMIC=0;
  lsmestimate GROUP        '------------------------------------------' 0 0;
  lsmestimate GROUP        ' Within-Group Time Main Effects           ' 0 0;
  lsmestimate GROUP*TIME ' Ctl:  6mth v Base, PrePand                ' -1    1    0   0   0  0/at PANDEMIC=0;
  lsmestimate GROUP*TIME ' Ctl: 12mth v 6mth, PrePand                '  0   -1    1   0   0  0/at PANDEMIC=0;
  lsmestimate GROUP*TIME ' Ctl: 12mth v Base, PrePand                ' -1    0    1   0   0  0/at PANDEMIC=0;
  lsmestimate GROUP        '                                          ' 0 0;
  lsmestimate GROUP*TIME ' Trt:  6mth v Base, PrePand                '  0    0    0  -1   1  0/at PANDEMIC=0;
  lsmestimate GROUP*TIME ' Trt: 12mth v 6mth, PrePand                '  0    0    0   0  -1  1/at PANDEMIC=0;
  lsmestimate GROUP*TIME ' Trt: 12mth v Base, PrePand                '  0    0    0  -1   0  1/at PANDEMIC=0;
  lsmestimate GROUP        ' ----------------------------------------' 0 0;
  lsmestimate GROUP        ' Group-Averaged Time Main Effects         ' 0 0;
  lsmestimate GROUP*TIME ' Group-Avg:  6mth v Base, PrePand          ' -.5  .5   0 -.5  .5  0/at PANDEMIC=0;
  lsmestimate GROUP*TIME ' Group-Avg: 12mth v 6mth, PrePand          '   0 -.5  .5   0 -.5 .5/at PANDEMIC=0;
  lsmestimate GROUP*TIME ' Group-Avg: 12mth v Base, PrePand          ' -.5   0  .5 -.5   0 .5/at PANDEMIC=0;
  lsmestimate GROUP        ' ----------------------------------------' 0 0;
run;

* ALSO INCLUDE ANOTHER SET OF THE ABOVE LSMESTIMATE COMMANDS REPLACING `/AT PANDEMIC=0` WITH `/AT PANDEMIC=1`;
```

```
*------------------------------------------------------------------------------------------*;
* STRATIFIED MODEL FOR PANDEMIC=0
*
* FOR THE PRE-PANDEMIC STRATIFIED MODEL, PANDEMIC=0 IS DECLARED IN THE SAS `WHERE` STATEMENT;
*------------------------------------------------------------------------------------------*;
  proc genmod data=<your data>;
   class GROUP TIME;
   model Y = GROUP|TIME/type3;
   where PANDEMIC=0;

* INCLUDE ONLY IF S(3,4). ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
    estimate ' Simple Group Main Effects            ' int 0;
    estimate " Trt v Ctl @ Base                     " GROUP -1 1;

* INCLUDE ONLY IF S(2,3,4). ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
    estimate ' Simple Group Main Effects            ' int 0;
    estimate " Trt v Ctl @ Base                     " GROUP -1 1 GROUP*TIME -1  0  1 0;
    estimate " Trt v Ctl @ 6mth                     " GROUP -1 1 GROUP*TIME  0 -1  0 1;
    estimate ' -----------------------------------' int 0;
    estimate ' Group*Time Interaction Effects       ' int 0;
    estimate " 2x2 Int: Trt v Ctl @Base- 6m         " GROUP*TIME 1 -1 -1  1;
    estimate ' -----------------------------------' int 0;
    estimate ' Within-Group Time Main Effects       ' int 0;
    estimate " Ctl:  6mth v Base                    " TIME -1  1 GROUP*TIME  -1 1  0 0;
    estimate '                                      ' int 0;
    estimate " Trt:  6mth v Base                    " TIME -1  1 GROUP*TIME   0 0 -1 1;
    estimate ' -----------------------------------' int 0;
    estimate ' Group-Averaged Time Main Effects     ' int 0;
    estimate " Group-Avg:  6mth v Base              " TIME -1  1;

* INCLUDE ONLY IF S(2,3) or S(2,3) AUGMENTED. ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
    estimate ' Simple Group Main Effects            ' int 0;
    estimate " Trt v Ctl @ Base                     " GROUP -1 1 GROUP*TIME -1  0 1 0;
    estimate " Trt v Ctl @ 6mth                     " GROUP -1 1 GROUP*TIME  0 -1 0 1;
    estimate ' -----------------------------------' int 0;
    estimate ' Group*Time Interaction Effects       ' int 0;
    estimate " 2x2 Int: Trt v Ctl @Base- 6m         " GROUP*TIME 1 -1 -1  1;
    estimate ' -----------------------------------' int 0;
    estimate ' Within-Group Time Main Effects       ' int 0;
    estimate " Ctl:  6mth v Base                    " TIME -1  1   GROUP*TIME -1 1  0 0;
    estimate '                                      ' int 0;
    estimate " Trt:  6mth v Base                    " TIME -1  1   GROUP*TIME  0 0 -1 1;
    estimate ' -----------------------------------' int 0;
    estimate ' Group-Averaged Time Main Effects     ' int 0;
    estimate " Group-Avg:  6mth v Base              " TIME -1  1;
```

```
* INCLUDE  ONLY IF S(1,2,3,4), S(1,2,3), S(1,2), S(1,2,3) Augmented, or S(1,2) Augmented;
* ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
  estimate ' Simple Group Main Effects              ' int 0;
  estimate " Trt v Ctl @ Base                       " GROUP -1 1 GROUP*TIME -1   0   0  1  0  0;
  estimate " Trt v Ctl @ 6mth                       " GROUP -1 1 GROUP*TIME  0  -1   0  0  1  0;
  estimate " Trt v Ctl @ 12mth                      " GROUP -1 1 GROUP*TIME  0   0  -1  0  0  1;
  estimate " Trt v Ctl @ 6mth+12mth: Time-Avg" GROUP -1 1 GROUP*TIME  0 -.5 -.5  0 .5 .5;
  estimate ' -----------------------------------' int 0;
  estimate ' Group*Time Interaction Effects         ' int 0;
  estimate " 2x2 Int: Trt v Ctl @Base- 6m           " GROUP*TIME 1 -1  0 -1  1 0;
  estimate " 2x2 Int: Trt v Ctl @  6m-12m           " GROUP*TIME 0  1 -1  0 -1 1;
  estimate " 2x2 Int: Trt v Ctl @Base-12m           " GROUP*TIME 1  0 -1 -1  0 1;
  estimate ' -----------------------------------' int 0;
  estimate ' Within-Group Time Main Effects         ' int 0;
  estimate " Ctl:  6mth v Base                      " TIME -1  1 0 GROUP*TIME -1  1 0  0  0 0;
  estimate " Ctl: 12mth v 6mth                      " TIME  0 -1 1 GROUP*TIME  0 -1 1  0  0 0;
  estimate " Ctl: 12mth v Base                      " TIME -1  0 1 GROUP*TIME -1  0 1  0  0 0;
  estimate '                                        ' int 0;
  estimate " Trt:  6mth v Base                      " TIME -1  1 0 GROUP*TIME  0  0 0 -1  1 0;
  estimate " Trt: 12mth v 6mth                      " TIME  0 -1 1 GROUP*TIME  0  0 0  0 -1 1;
  estimate " Trt: 12mth v Base                      " TIME -1  0 1 GROUP*TIME  0  0 0 -1  0 1;
  estimate ' -----------------------------------' int 0;
  estimate ' Group-Averaged Time Main Effects       ' int 0;
  estimate " Group-Avg:  6mth v Base                " TIME -1  1 0;
  estimate " Group-Avg: 12mth v 6mth                " TIME  0 -1 1;
  estimate " Group-Avg: 12mth v Base                " TIME -1  0 1;
  run;
```

```
*---------------------------------------------------------------------------------*;
* STRATIFIED MODEL FOR PANDEMIC=1
*
* FOR THE PANDEMIC-ERA STRATIFIED MODEL, PANDEMIC=1 IS DECLARED IN THE SAS `WHERE` STATEMENT;
*---------------------------------------------------------------------------------*;
  proc genmod data=<your data>;
   class GROUP TIME;
   model Y = GROUP|TIME/type3;
   where PANDEMIC=1;

* INCLUDE ONLY IF S(1,2,3). ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
   estimate ' Simple Group Main Effects           ' int 0;
   estimate " Trt v Ctl @ 6mth                    " GROUP -1 1 GROUP*TIME  -1   0   1   0;
   estimate " Trt v Ctl @ 12mth                   " GROUP -1 1 GROUP*TIME   0  -1   0   1;
   estimate " Trt v Ctl @ 6mth+12mth: Time-Avg    " GROUP -1 1 GROUP*TIME -.5 -.5  .5  .5;
   estimate ' ----------------------------------- ' int 0;
   estimate ' Group*Time Interaction Effects      ' int 0;
   estimate " 2x2 Int: Trt v Ctl @  6m-12m        " GROUP*TIME 1 -1 -1 1;
   estimate ' ----------------------------------- ' int 0;
   estimate ' Within-Group Time Main Effects      ' int 0;
   estimate " Ctl: 12mth v 6mth                   " TIME -1 1 GROUP*TIME  -1 1   0 0;
   estimate '                                     ' int 0;
   estimate " Trt: 12mth v 6mth                   " TIME -1 1 GROUP*TIME    0 0  -1 1;

* INCLUDE ONLY IF S(1,2,3,4), S(2,3,4), S(3,4), S(1,2,3) AUGMENTED, or S(2,3) AUGMENTED;
* ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
   estimate ' Simple Group Main Effects           ' int 0;
   estimate " Trt v Ctl @ Base                    " GROUP -1 1 GROUP*TIME -1   0   0   1   0   0;
   estimate " Trt v Ctl @ 6mth                    " GROUP -1 1 GROUP*TIME  0  -1   0   0   1   0;
   estimate " Trt v Ctl @ 12mth                   " GROUP -1 1 GROUP*TIME  0   0  -1   0   0   1;
   estimate " Trt v Ctl @ 6mth+12mth: Time-Avg    " GROUP -1 1 GROUP*TIME  0 -.5 -.5   0  .5  .5;
   estimate ' ----------------------------------- ' int 0;
   estimate 'Group*Time Interaction Effects       ' int 0;
   estimate " 2x2 Int: Trt v Ctl @Base- 6m        " GROUP*TIME 1 -1  0 -1  1 0;
   estimate " 2x2 Int: Trt v Ctl @  6m-12m        " GROUP*TIME 0  1 -1  0 -1 1;
   estimate " 2x2 Int: Trt v Ctl @Base-12m        " GROUP*TIME 1  0 -1 -1  0 1;
   estimate ' ----------------------------------- ' int 0;
   estimate ' Within-Group Time Main Effects      ' int 0;
   estimate " Ctl:  6mth v Base                   " TIME -1  1 0 GROUP*TIME -1  1 0  0  0 0;
   estimate " Ctl: 12mth v 6mth                   " TIME  0 -1 1 GROUP*TIME  0 -1 1  0  0 0;
   estimate " Ctl: 12mth v Base                   " TIME -1  0 1 GROUP*TIME -1  0 1  0  0 0;
   estimate '                                     ' int 0;
   estimate " Trt:  6mth v Base                   " TIME -1  1 0 GROUP*TIME  0  0 0 -1  1 0;
   estimate " Trt: 12mth v 6mth                   " TIME  0 -1 1 GROUP*TIME  0  0 0  0 -1 1;
   estimate " Trt: 12mth v Base                   " TIME -1  0 1 GROUP*TIME  0  0 0 -1  0 1;
   estimate ' ----------------------------------- ' int 0;
   estimate ' Group-Averaged Time Main Effects    ' int 0;
   estimate " Group-Avg:  6mth v Base             " TIME -1  1 0;
   estimate " Group-Avg: 12mth v 6mth             " TIME  0 -1 1;
   estimate " Group-Avg: 12mth v Base             " TIME -1  0 1;
```

```
* INCLUDE ONLY IF S(2,3). ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
   estimate ' Simple Group Main Effects                ' int 0;
   estimate " Trt v Ctl @ 6mth                         " GROUP -1 1 GROUP*TIME  -1   0   1  0;
   estimate " Trt v Ctl @ 12mth                        " GROUP -1 1 GROUP*TIME   0  -1   0  1;
   estimate " Trt v Ctl @ 6mth+12mth: Time-Avg         " GROUP -1 1 GROUP*TIME -.5 -.5  .5 .5;
   estimate ' -----------------------------------' int 0;
   estimate ' Group*Time Interaction Effects           ' int 0;
   estimate " 2x2 Int: Trt v Ctl @   6m-12m            " GROUP*TIME  1 -1  -1 1;
   estimate ' -----------------------------------' int 0;
   estimate ' Within-Group Time Main Effects           ' int 0;
   estimate " Ctl: 12mth v 6mth                        " TIME -1 1 GROUP*TIME  -1 1   0 0;
   estimate '                                          ' int 0;
   estimate " Trt: 12mth v 6mth                        " TIME -1 1 GROUP*TIME   0  0 -1 1;
   estimate ' -----------------------------------' int 0;
   estimate ' Group-Averaged Time Main Effects         ' int 0;
   estimate " Group-Avg: 12mth v 6mth                  " TIME -1 1;

* INCLUDE ONLY IF S(1,2). ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
   estimate ' Simple Group Main Effects                ' int 0;
   estimate " Trt v Ctl @ 12mth                        " GROUP -1 1;

* INCLUDE ONLY FOR S(1,2) AUGMENTED. ONLY THE EFFECTS THAT CAN BE ESTIMATED ARE INCLUDED;
      estimate ' Simple Group Main Effects                ' int 0;
      estimate " Trt v Ctl @ Base                         " GROUP -1 1  GROUP*TIME -1  0  1  0;
      estimate " Trt v Ctl @ 12mth                        " GROUP -1 1  GROUP*TIME  0 -1  0  1;
      estimate ' -----------------------------------' int 0;
      estimate ' Group*Time Interaction Effects           ' int 0;
      estimate " 2x2 Int: Trt v Ctl @Base-12m             "           GROUP*TIME  1 -1 -1  1;
      estimate ' -----------------------------------' int 0;
      estimate ' Within-Group Time Main Effects           ' int 0;
      estimate ' -----------------------------------' int 0;
      estimate " Ctl: 12mth v Base                        " TIME -1 1  GROUP*TIME  -1  1  0  0 ;
      estimate '                                          ' int 0;
      estimate " Trt: 12mth v Base                        " TIME -1 1  GROUP*TIME   0  0 -1  1 ;
      estimate ' -----------------------------------' int 0;
      estimate ' Group-Averaged Time Main Effects         ' int 0;
      estimate " Group-Avg: 12mth v Base                  " TIME -1 1;
run;
```