Appendices

These Appendices are intended to provide some light on theoretical aspect of some results observed in this article that some readers may find very useful, but that may not be of interest to some other readers. These Appendices can be read in their entirety, selectively, or not at all.

Appendix 1 focuses on why the sample size for multiple timepoint assessments for correlation=0.5 under the correlation structure of compound symmetry for the mean difference type of contrast coincides with the sample size with single time point assessment.

Appendix 2 outlines how the required sample size is larger/smaller for multiple timepoint assessment compared to single time point assessment if correlation<0.5 or correlation>0.5 under compound symmetry correlation structure for mean difference type of contrast.

Appendix 3 talks about the flip that happens in the sample size for AR1 correlation structure under mean over time contrast where the sample size increases with increasing number of time points for correlation > 0.35

Appendix 1. Sample size with correlation=0.5 under compound symmetry type of correlation structure for multiple timepoint assessment with the mean difference type of contrast coincides with single time point assessment

This is primarily because we consider equal variance, and below theoretical derivations show how this equality is achieved. This result or observation may not hold true if we differ from the equal variance assumption.

Consider a case of 3 timepoints,

Let Y_1, Y_2, Y_3 and X_1, X_2, X_3 be the assessments at baseline, mid study and end of the study for test and control respectively.

The factor that differs in single timepoint and multiple timepoint sample size calculation is $\frac{\sigma^2}{(\bar{Y}-\bar{X})^2}$ and $\frac{\sigma_c^2}{\hat{\psi}_c^2}$ respectively.

Now $\bar{Y} - \bar{X}$ is the difference in the effect produced by intervention which would be

(i)
$$\bar{Y} - \bar{X} = (\bar{Y}_3 - \bar{Y}_1) - (\bar{X}_3 - \bar{X}_1)$$

For the diff contrast

(ii)
$$\hat{\psi}_c = (-1, 0, 1)\begin{bmatrix} \bar{Y}_1 - \bar{X}_1 \\ \bar{Y}_2 - \bar{X}_2 \\ \bar{Y}_3 - \bar{X}_3 \end{bmatrix} = (\bar{Y}_3 - \bar{Y}_1) - (\bar{X}_3 - \bar{X}_1) = \bar{Y} - \bar{X} \text{ , from (i)}$$

Also,

(iii)
$$\sigma_c^2 = \left[\sum_{i=1}^{t} c_i^2 \sigma_i^2 + 2\sum_{i<j}^{t} c_i\, c_j\, \sigma_{ij}\right] = \sigma_1^2 + \sigma_3^2 + 2\big(-1\,(\sigma_{13})\big) = 2\sigma^2 - 2\rho\sigma^2 = 2\sigma^2(1-\rho),$$

Since we have assumed equal variance, covariance $\sigma_{13} = \rho\sigma_1\sigma_3 = \rho\sigma^2$

Now for $\rho = 0.5$ we get,

(iv)

$$\sigma_c^2 = 2\sigma^2(1 - 0.5) = \sigma^2$$

So from (ii) and (iv) we could see that the numerator and denominator in sample size calculation with multiple timepoint assessment coincides with that of single timepoint assessment under compound symmetry correlation structure with correlation=0.5 and variances assumed to be equal.

Appendix 2. Sample size increases/decreases for multiple timepoint assessment compared to single time point assessment if correlation<0.5 or correlation>0.5 under compound symmetry correlation structure for mean difference type of contrast

The numerator in sample size calculation with multiple timepoint assessment would be same as that for single timepoint assessment under compound symmetry correlation structure for mean difference type of contrast as shown in (ii).
Consider the σ_c^2 as derived in (iii);
For $\rho > 0.5, \sigma_c^2 = 2\sigma^2(1 - \rho) < \sigma^2$ and so the sample size is lesser in this case.
For $\rho < 0.5, \sigma_c^2 = 2\sigma^2(1 - \rho) > \sigma^2$ and so, the sample size is greater in this case.

Appendix 3. Sample size for AR1 under mean over time contrast increases with increasing number of time points for correlation > 0.35

This is majorly due to the variance component σ_c^2 in the multiple timepoint assessment. The variance component σ_c^2 takes the following form for the AR1 type of correlation structure under mean over time contrast for time t.

$$\sigma_c^2 = \frac{\sigma^2}{t-1}\left[t - \left(\frac{2}{t-1}\right)(\rho + 2\rho^2 + 3\rho^3 + 4\rho^4 + \cdots + (t-1)\rho^{t-1})\right]$$

Below table shows the variance component for 4 timepoint assessment vs 10 timepoint assessment over different correlation using common (SD) of 3.6 points. We can clearly see how the variance component for the 4 timepoint assessment starts decreasing compared to 10 timepoint assessment after the flipping point of rho=0.45. This phenomenon led to sample size increase with increasing number of time points when correlation > 0.35 for AR(1) correlation structure under mean over time contrast.

rho	σ_c^2 with 10 timepoint assessment (t1)	σ_c^2 with 4 timepoint assessment (t2)	Ratio=t1/t2
0.2	14.3	16.40448	0.871713
0.3	14.20411	15.66432	0.906781
0.35	14.13505	15.19596	0.930185
0.4	14.04504	14.65344	0.958481
0.45	13.92611	14.03028	0.992575
0.5	13.76688	13.32	1.033549
0.55	13.55108	12.51612	1.08269

0.6	13.25563	11.61216	1.14153
0.65	12.84799	10.60164	1.211887
0.7	12.28272	9.47808	1.295908
0.75	11.49706	8.235	1.396121
0.8	10.40518	6.86592	1.515483
0.85	8.891091	5.36436	1.657438
0.9	6.799649	3.72384	1.825978

Clinical Example: Practical Use of the Proposed Sample Size Approach

Study objective & Design

A randomized controlled trial is planned to evaluate whether a new antihypertensive treatment produces a sustained reduction in systolic blood pressure (SBP) over time. Participants are followed for 2 years, with SBP measured at baseline and every 4 months, resulting in 7 total measurement occasions.

Estimand of interest

The primary estimand is the mean over time contrast, defined as the average difference in SBP between treatment groups across all post-baseline visits. This estimand is appropriate when long-term disease control is of clinical importance, rather than the effect at a single visit.

Assumptions for sample size calculation:

- Expected treatment effect difference Λ' (mmHg) = [0, 4.7, 4.8, 5.0, 5.1, 5.2, 5.2], assuming the 2 groups have same SBP at baseline.
- Standard deviation at each visit σ_i^2: 10 mmHg
- Covariance structure: AR(1) with adjacent visit correlation, $\rho = 0.4$
- Type I error: $\alpha = 0.05$ (two-sided)
- Power: 80%
- Mean over time contrast $C' = [-1, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}]$

Implementation and interpretation

With the above specified follow-up schedule, assumed covariance structure, treatment effect, variability, and using the equation 13 presented in the main manuscript along with the accompanying R software (see Software Availability in main manuscript), one can derive the sample size required to meet the example objective under given study design and estimand of interest.