Thesis notes
Assemble to a complete thesis

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Contents

1 Stratification

We know that not taking stratification into account when modelling yields incorrect SE's. In (Bugni et al., 2018) they develop a method to take stratification into account for the t-test. This is also mentioned in the FDA covariate adjustment guidance document from May 2023. A generalisation of the results in (Bugni et al., 2018) is found in (Wang et al., 2023).

2 Simple example

To gain an intuition for the effect of modelling the stratified randomization we posit the simplest setup possible and write up an explicit formula for the correction term in the asymptotic variance presented in (Wang et al., 2023). To this end, assume a binary endpoint Y , binary treatment A and a binary stratification variable $X = S$.
The target estimand is the marginal treatment effect

$$\Delta = \mathbb{E}[Y \mid A = 1] - \mathbb{E}[Y \mid A = 0].$$

The influence function for the marginal ATE in the non-parametric setting is given by example 3.4.3 in (Kennedy, 2022),

$$\mathbb{IF}(\Delta) = \frac{A}{\pi}(Y - \mathbb{E}[Y \mid A = 1]) - \frac{1 - A}{1 - \pi}(Y - \mathbb{E}[Y \mid A = 0]).$$

The asymptotic variance of $\hat{\Delta}$ under stratified randomization is given by equation 1 in (Wang et al., 2023),

$$V = \tilde{V} - V_{\text{strata}} = \tilde{V} - \frac{1}{\pi(1-\pi)}\mathbb{E}\left[\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S)]^2\right].$$

where $\tilde{V}$ is the standard asymptotic variance under simple randomization given by $\mathbb{E}(\mathbb{IF}(\Delta)^2)$ and the last term is denoted the correction term.
We can now compute the correction factor

$$\mathbb{E}\left[\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S)]^2\right].$$

2.1 Calculation

The tower property gives an inner, inner expectation which we can compute:

$$\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S] = \mathbb{E}[\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S, A] \mid S].$$

So for notational purposes, let $\mu_1 = \mathbb{E}[Y \mid A = 1]$ and $\mu_0 = \mathbb{E}[Y \mid A = 0]$. The inner, inner expectation becomes

$$\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S, A] = (A-\pi)\left(\frac{A}{\pi}(\mathbb{E}[Y \mid S, A] - \mu_1) - \frac{1-A}{1-\pi}(\mathbb{E}[Y \mid S, A] - \mu_0)\right).$$

Writing out the expectations on the left hand side of the above utilizing that A are binary yields

$$\mathbb{E}[Y \mid S, A] = A\mathbb{E}[Y \mid S, A = 1] + (1-A)\mathbb{E}[Y \mid S, A = 0] = A\mu_{X,1} + (1-A)\mu_{X,0}.$$

Inserting and simplifying gives

$$\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S, A] = \frac{1-\pi}{\pi}A(\mu_{X,1} - \mu_1) + \frac{\pi}{1-\pi}(1-A)(\mu_{X,0} - \mu_0)$$

We now take the expectation given S and using balance within strata, i.e, $\mathbb{E}[A \mid S] = \pi$.

$$\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S] = \mathbb{E}[\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S, A] \mid S] = (1-\pi)(\mu_{X,1} - \mu_1) + \pi(\mu_{X,0} - \mu_0)$$

Defining $\pi_{sa} = P(Y = 1 \mid A = a, S = s)$ we reach the final expression by squaring and computing the expectation

$$\mathbb{E}\left[\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S)]^2\right] = \mathbb{E}[((1-\pi)(\mu_{X,1} - \mu_1) + \pi(\mu_{X,0} - \mu_0))^2]$$

That is,

$$\begin{aligned} V_{\text{strata}} &= \frac{1}{\pi(1-\pi)}\mathbb{E}\left[\mathbb{E}[(A-\pi)\mathbb{IF}(\Delta) \mid S)]^2\right] \\ &= \frac{1-\pi}{\pi}\mathbb{E}[(\mu_{X,1} - \mu_1)^2] + \frac{\pi}{1-\pi}\mathbb{E}[(\mu_{X,0} - \mu_0)^2] + 2\mathbb{E}[(\mu_{X,1} - \mu_1)(\mu_{X,0} - \mu_0)] \end{aligned}$$

Finally

$$\begin{aligned} V_{\text{strata}} = \frac{1-\pi}{\pi}&\left(p_X\pi_{11}^2 + (1-p_X)\pi_{01}^2 - \mu_1^2\right) \\ +\frac{\pi}{1-\pi}&\left(p_X\pi_{10}^2 + (1-p_X)\pi_{00}^2 - \mu_0^2\right) \\ &+2(p_X\pi_{11}\pi_{10} + (1-p_X)\pi_{01}\pi_{00}) \end{aligned}$$

where $p_X = P(X = 1)$.

3 Adjusting for stratification indicators

When setting up an RCT we often need to prespecify an analysis plan and deciding baseline covariates we want to adjust for in our analysis. This is not a trivial task (mention stuff). When the trial uses a stratified randomization procedure we can look towards corollary 1 in (Wang et al., 2023). Corollary 1 shows that if we adjust for indicators for the randomization strata and treatment-by-randomization strata interaction terms, then the correction term in the variance becomes zero, i.e., $V = \tilde{V}$. This corollary matches our intuition, since including information of the stratification in the model should express the same information as not including this information, but using the correction term in the variance.

We show, that this is indeed the case in the setting where we target the marginal ATE, but still include information from covariates $X = S$ we can gain extra efficiency in the estimation of the average treatment effect Δ since $A \perp\!\!\!\perp X$. The independence of treatment and baseline covariates is given by the simple randomization. By example 5.4 in (Tsiatis, 2006) we know the efficient influence function for this case:

$$\begin{aligned}
\mathbb{EIF}(\Delta) &= \mathbb{IF}(\Delta) - \Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp}) \\
&= \mathbb{IF}(\Delta) - \Big(\frac{A-\pi}{\pi}[\mu_{X,1} - \mu_1] + \frac{A-\pi}{1-\pi}[\mu_{X,0} - \mu_0]\Big) \\
&= \Big(\frac{A}{\pi}Y - \frac{A-\pi}{\pi}\mathbb{E}[Y \mid A=1, X]\Big) - \Big(\frac{1-A}{1-\pi}Y + \frac{A-\pi}{1-\pi}\mathbb{E}[Y \mid A=0, X]\Big) - \Delta.
\end{aligned}$$

Where $\mathcal{J}$ is the tangent space of semiparametric models in this setup.
Corollary 1 in (Wang et al., 2023) tells us that the correction term should be zero. To see this in practice, let us compute the asymptotic variance of $\hat{\Delta}$ in this case while utilizing that

$$(\mathbb{IF}(\Delta) - \Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp}) \perp \mathbb{IF}(\Delta)$$

Pythagoras now yields:

$$\begin{aligned}
\tilde{V}_{\text{eff}} &= \mathbb{E}[\mathbb{EIF}(\Delta)^2] \\
&= \mathbb{E}[(\mathbb{IF}(\Delta) - \Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp}))^2] \\
&= \big\|\mathbb{IF}(\Delta) - \Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp})\big\|^2 \\
&= \|\mathbb{IF}(\Delta)\|^2 - \big\|\Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp})\big\|^2 \\
&= \mathbb{E}[\mathbb{IF}(\Delta)^2] - \mathbb{E}[(\Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp}))^2] \\
&= \tilde{V} - \mathbb{E}[(\Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp}))^2]
\end{aligned}$$

We want to show that $V_{\text{strata}_{\text{eff}}} = 0$ or equally

$$\mathbb{E}[(\Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp}))^2] = V_{\text{strata}}.$$

This is easily seen, as

$$\mathbb{E}[(\Pi(\mathbb{IF}(\Delta) \mid \mathcal{J}^{\perp}))^2] = \mathbb{E}\left[\Big(\frac{A-\pi}{\pi}[\mu_{X,1} - \mu_1] + \frac{A-\pi}{1-\pi}[\mu_{X,0} - \mu_0]\Big)^2\right]$$

$$= \frac{1-\pi}{\pi}\mathbb{E}[(\mu_{X,1} - \mu_1)^2] + \frac{\pi}{1-\pi}\mathbb{E}[(\mu_{X,0} - \mu_0)^2] + 2\mathbb{E}[(\mu_{X,1} - \mu_1)(\mu_{X,0} - \mu_0)] = V_{\text{strata}}$$

Which is exactly what we wanted.

4 Simulation study

* Implement a small simulation study to see if we get the correct variance.
* Use less than 100 patients in each trial.

5 Simulation study - naive case

* See quarto document?

6 Make my code a package in R

* Takes a week / WRITE IT OVER CHRISTMAS before defence.
* Packages are important?
* Make an easy way to make simulations for trials to test power gain
* Maybe also an interactive site on my website?

References

Bugni, F. A., Canay, I. A., & Shaikh, A. M. (2018). Inference under covariate-adaptive randomization. *Journal of the American Statistical Association*, *113*(524), 1784–1796.

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Tsiatis, A. A. (2006). *Semiparametric theory and missing data*. Springer.

Wang, B., Susukida, R., Mojtabai, R., Amin-Esmaeili, M., & Rosenblum, M. (2023). Model-robust inference for clinical trials that improve precision by stratified randomization and covariate adjustment. *Journal of the American Statistical Association*, *118*(542), 1152–1163.