Identifying Treatment Effects using Trimmed Means when Data are Missing Not at Random

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Abstract

Patients often discontinue treatment in a clinical trial because their health condition is not improving. Consequently, the patients still in the study at the end of the trial have better health outcomes on average than the initial patient population would have had if every patient had completed the trial. If we only analyze the patients who complete the trial, then this “missing data problem” biases the estimator of a medication’s efficacy because study outcomes are missing not at random (MNAR). One way to overcome this problem - the trimmed means approach for missing data - sets missing values as the worst observed outcome and then trims away a fraction of the distribution from each treatment arm before calculating differences in treatment efficacy (Permutt 2017, Pharmaceutical statistics 16.1: 20-28). In this paper we derive sufficient and necessary conditions for when this approach can identify the average population treatment effect. Numerical studies show the trimmed means approach’s ability to effectively estimate treatment efficacy when data are MNAR and missingness is strongly associated with an unfavorable outcome, but trimmed means fail when data are missing at random (MAR). If the reasons for discontinuation in a clinical trial are known analysts can improve estimates with a combination of multiple imputation (MI) and the trimmed means approach when the assumptions of each hold. We compare the methodology to existing approaches using data from a clinical trial for chronic pain. When the assumptions are justifiable, using trimmed means can help identify treatment effects notwithstanding MNAR data.

Keywords: Missing Data, Trimmed Means, Clinical Trials, Estimand

1 Introduction

Restricting statistical analysis to patients that complete a clinical trial can lead to biased results1. Patients with unfavorable endpoints often discontinue the trial prematurely and thus the remaining patients no longer provide a truly representative sample of patients, even if the original sample did. This situation can be viewed as a missing data problem - the endpoints are not measured for the patients who have left the study and are thus labeled as missing. There is no consensus on how best to adjust a statistical analysis for missing data. This is due in part because the reason for missing data impacts the choice of analytical methods to use. The best understood situation is when the data are missing at random (MAR)2. This means that one observes all the data necessary to explain the missingness in the data - i.e. the missing values themselves did not...
contribute to the fact that they are missing. This, of course, is not only an untestable assumption, but in many settings, it is an unrealistic one. Its complementary situation, when data are missing not at random (MNAR), occurs in clinical trials. An example of this is trials of chronic pain, where subjects are more likely to leave the study if they experience little or no decrease in pain. Consequently, the outcomes of those who complete the study differ from those who do not, often even when accounting for observed information. In these situations, ignoring the violations of the assumptions underpinning popular missing data methods designed for MAR data, such as multiple imputation\(^3\) and inverse probability weighting\(^4\), leads to biases that make the analyses inadequate and of little scientific value.

The paucity of data analytic methods for when the data are MNAR may contribute to the widespread use of inappropriate methods. The National Research Council (NRC) report on missing data suggests two general paths forward when data are MNAR: Selection Models and Pattern-Mixture Models\(^5\). Both of these models are limited in that they rely on parameters that cannot be inferred from the observed data. Therefore, identification of treatment effects using these models is not possible. This limitation is emphasized by Little\(^6\) who highlights that all MNAR models are subject to a fundamental lack of identification. The shadow variable approach of Miao & Tchetgen Tchetgen can identify causal effects under MNAR\(^7\); however, it relies on the presence of a surrogate outcome - a shadow variable - that is closely related to the missing outcome and unrelated to why the missing outcome is unobserved. One may not observe such a variable in the clinical trial setting. Jump to reference imputation\(^8\) is a popular approach to handling MNAR data where the missing outcomes of patients in the experimental treatment arm are imputed using observed outcomes from the reference arm. The logic of this approach makes intuitive sense, in the experimental arm MNAR dropouts have worse outcomes than those who complete the study. So to reflect this difference one can leverage the worse outcomes of reference/reference arm for imputations of experimental dropouts. The main drawback for the MNAR setting is that missing outcomes in the reference arm are imputed by reference completers which effectively assumes MAR. If reference arm dropouts are MNAR, then reference imputations may be optimistic and the treatment effect can be underestimated. Especially in placebo-controlled trials, one generally expects more lack of efficacy dropouts in the reference arm which could be problematic for jump to reference unless initial measurements leveraged for imputations reveal the poor outcome trajectory.

The “trimmed means approach” for missing data was first introduced by Li and Permutt\(^9\). The method is designed for settings where missing values can be assumed to be poor health outcomes that are the continuous endpoints of the study; precisely the example introduced above. We focus on this method in the remainder of the paper. The trimmed means approach is simple to implement in a comparative trial. The final statistic is the arithmetic mean after trimming the poor performing parts of the distribution in each arm of the study, after assigning a value to the missing outcomes that is worse than the worst observed outcome. Applying this approach only requires the ability to assign a rank to all outcomes and ranks missing outcomes at the tail end of the distribution prior to trimming. The trimmed means approach can be extended to include covariates such as in an ANCOVA and can be applied in mixed models for repeated measures (MMRM)\(^10\). The trimmed-means-approach was designed to estimate an estimand different than most standard analyses. Instead of estimating treatment difference in the whole study population, the approach estimates the treatment difference in a subset of the best performing patients since those performing poorly are trimmed out of the analysis. As a result, some of the data is lost, and that is the price one pays for obtaining an analysis that accommodates MNAR data. The trimmed-means-approach was evaluated under various missing data generating mechanisms\(^11\), which reveals some of its limitations.
The rest of the paper concentrates on extending the utility of the trimmed-means-approach for missing data. Section 2 describes the trimmed means approach and extends its use to a combination with multiple imputation. Section 3 discusses the estimand and provides a proof for settings under which the trimmed means approach can identify the population treatment effect. Section 4 evaluates the finite sample properties of the approach in a numerical study under various missing data mechanisms. Section 5 provides recommendations on how to apply the approach in the context of a randomized clinical trial for a chronic pain medication. Section 6 concludes the article with a discussion.

2 Statistical Methods

2.1 The Trimmed Means Estimator

In 2017, Permutt and Li introduced the trimmed means estimator. They provide a thorough motivation of the approach as well as how to implement it in practice. Mehrotra et al. demonstrate an implementation of the approach in SAS. This approach does not rely on any parametric model or imputation of the missing values; it only depends on the ability to rank outcomes. The trimmed means approach for missing data utilizes one sided trimmed means. Consider a continuous outcome \( Y_i \) for observation \( i \). The one sided trimmed mean is an L-estimator defined as:

\[
\hat{\mu}_T = \frac{1}{n_T} \sum_{i:Y_i > \hat{F}^{-1}(\alpha)} Y_i
\]

The above is simply the average of the observations that fall above the quantile \( \hat{F}^{-1}(\alpha) \) of the empirical distribution function of \( Y_i \) where \( \alpha \) represents the proportion of trimmed outcomes. For example, \( \alpha = 0.3 \) represents trimming away the bottom 30% of the distribution. Here, \( n_T = \sum_{i=1}^{n} 1(\hat{F}^{-1}(\alpha)) \) is the sample size after trimming. The expectation of the trimmed mean is the population trimmed mean:

\[
\mu_T = E[Y|Y > F^{-1}(\alpha)] = \frac{1}{1 - \alpha} \int_{F^{-1}(\alpha)}^{\infty} yf(y)dy
\]

Note that for this example above, poor outcomes correspond to low values of \( Y \), so the lower part of the distribution is trimmed. This could be switched based on the clinical context. For example, in pain trials a decrease in pain intensity is a good outcome, so one would rather trim away the upper part of the distribution.

To implement this approach, first consider three observed variables: \( A \) a binary indicator for treatment, \( R \) a binary missing data indicator, and the clinical outcome \( Y \) which is a continuous value when \( R = 1 \) and is missing when \( R = 0 \). Operationally, the first step of the trimmed means approach is to remove the missing data by ranking all missing outcomes as slightly worse than the poorest observed outcome in the trial. To do so one defines a new outcome denoted by \( U \) for each subject \( i \):

\[
U_i = \begin{cases} 
Y_i & \text{if } R_i = 1 \\
\min(Y) - \epsilon & \text{if } R_i = 0 \text{ for } \epsilon > 0 
\end{cases}
\]

Note the above corresponds to low values representing poor outcomes. If high values of the outcome reflected poor values then if \( R = 0 \) the missing outcomes would be set to \( \max(Y) + \epsilon \). After ranking, \( \alpha \) proportion of each treatment arm is trimmed away from the end of the distribution of \( U \).
associated with poor outcomes. The analyst has some flexibility in determining $\alpha$, the proportion of data trimmed from each distribution, before calculating the treatment effect. This value can be fixed a priori with a value of $\alpha$ chosen that anticipates the amount of missing data. Alternatively, trimming can be adaptive and chosen to be the maximum between the proportions of missing data in each arm. Thus the values that the missing observations were set to are never actually used in the analysis, but do serve the important function of informing the quantiles at which each distribution is to be trimmed. After trimming, then calculate the mean of the remaining 100 \times (1 - \alpha)\% observations in each arm $\hat{\mu}_1$ and $\hat{\mu}_0$. The final estimate is obtained by taking the difference of these trimmed means between each arm: $\hat{\mu}_{T\Delta} = \hat{\mu}_1 - \hat{\mu}_0$.

Inference can be conducted via a permutation test that conditions on the observed data and randomly permutes the treatment assignments. The resulting permutation distribution of treatment differences formed under the null hypothesis can be used to determine significant differences and confidence intervals. To reject the null hypothesis of no treatment difference, the point estimate should fall above the upper 2.5th percentile of the permutation distribution. If $\hat{\mu}_{T\Delta}$ is the treatment difference calculated after trimming, a 95% confidence interval can be constructed by adding the 97.5th and 2.5th percentiles of the permutation distribution to $\mu_{T\Delta}$. This can be generalized for any significance level $\gamma$ such that $(\hat{\mu}_{T\Delta} - y_\gamma/2, \hat{\mu}_{T\Delta} + y_{1-\gamma/2})$ yields a $(1 - \gamma)\%$ confidence interval where $y_\gamma$ is the $\gamma$ percentile of the permutation distribution. Since these confidence intervals are constructed using the permutation distribution generated under the null hypothesis, the intervals will be conservative when the null hypothesis is false.

### 2.2 Combining Trimmed Means with Multiple Imputation

In well conducted clinical trials, the reason for study discontinuation is collected for each patient who drops out of the study. Treating certain types of dropout as poor outcomes and ranking them at the low end of the distribution, as the trimmed means approach does, would lead to biases. Knowing the reason for dropping out of a study, and using that information, should lead to more precise analyses. To that end, consider the expanded indicator:

$$ R = \begin{cases} 
    r_1 & \text{if } Y \text{ observed} \\
    r_2 & \text{if MAR or MCAR} \\
    r_3 & \text{if MNAR}
\end{cases} $$

Assume the complete data of $Y$ is partitioned into the observed and missing components as follows $Y = [Y_{r_1}, Y_{r_2}, Y_{r_3}]$ which denote the observed, missing at random, and missing not at random components of $Y$ respectively. Here we propose imputing $Y_{r_2}$ and trimming $Y_{r_3}$. We can perform multiple imputation of $Y_{r_2}$ when the conditional distribution $f(Y_{r_2}|Y_{r_1} = y_{r_1}, A, X)$ is a valid imputation model given the MAR assumption. Here $y_{r_1}$ denotes the observed outcomes, $A$ is the treatment assignment, and $X$ is a matrix of auxiliary covariates that may or may not be available and of use for imputations. Using this conditional distribution, one can draw $m$ samples for the MAR and MCAR data $Y^{(1)}_{r_2}, Y^{(2)}_{r_2}, \ldots, Y^{(m)}_{r_2}$ to derive a set of data that is now complete for $Y_{r_2}$ where missing values $Y_{r_3}$ remain. Let $\hat{\mu}_{T\Delta} = \hat{\mu}_{T\Delta} (Y_{r_1}, Y_{r_2}, \mathbb{1}(R = r_3))$ denote the trimmed means statistic given that complete data on $Y_{r_2}$ were available. Note we do not need to observe $Y_{r_3}$ since the trimmed means approach will trim these observations out of the analysis. Multiple imputation relies on the asymptotically normal distribution of $\hat{\mu}_{T\Delta}$, which applies to the trimmed mean. Since data on $Y_{r_2}$ are missing, the imputed data are utilized to calculate trimmed means estimates of the form $\hat{\mu}_{T\Delta}^{(i)} = \hat{\mu}_{T\Delta} (Y_{r_1}, Y_{r_2}^{(i)}, \mathbb{1}(R = r_3))$ for the $m$ imputed datasets. Lastly, we
Rubin’s rules [3] to summarize the results of the trimmed means applied to each partially imputed dataset.

\[
\bar{\mu}_{T\Delta} = \frac{1}{m} \sum_{\ell=1}^{m} \mu_{T\Delta}^{(\ell)} = \frac{1}{m} \sum_{\ell=1}^{m} \bar{\mu}^{(\ell)} - \mu_{T0}^{(\ell)}
\]

\[
Var(\bar{\mu}_{T\Delta}) = \frac{1}{m} \sum_{\ell=1}^{m} (\sigma^{(\ell)})^2 + \left(1 + \frac{1}{m}\right) \left(\frac{1}{m-1} \sum_{\ell=1}^{m} (\mu_{\Delta}^{(\ell)} - \bar{\mu}_{T\Delta})^2\right)
\]

Where \(\sigma^{(\ell)}\) is the estimated standard error of the trimmed means estimate in the \(\ell\)th imputed dataset. This combination approach is only valid if all unobserved values of \(Y_{r_3}\) fall below the quantile of the distributions that are trimmed, a condition discussed in the subsequent section.

3 Properties of the Estimand

3.1 Equivalence to the Population Treatment Effect

We focus on a randomized clinical trial, where the estimand of interest is the treatment difference in the population means of a clinical endpoint. Consider counterfactual outcomes \(Y_a\) where \(a \in 0, 1\) indicates potential treatment assignments. In addition, \(A \in 0, 1\) is the binary indicator for observed treatment in the trial. Denote \(U_a\) as the counterfactual version of the composite outcome defined in section 2. The trimmed means estimand is most similar to a composite estimand, using the terminology of the ICH E9 addendum 15. The trimmed means estimand in counterfactual notation is

\[
E[U_1|U_1 > F_{U_1}^{-1}(\alpha)] - E[U_0|U_0 > F_{U_0}^{-1}(\alpha)] = E[Y_1] - E[Y_0]
\]

The advantage of the trimmed means approach’s composite estimand is that it gives us a strategy for handling the missing data; however, the main drawback of using a composite estimand is that the clinical relevance can be unclear. In may be difficult and unfamiliar to interpret an estimated treatment effect in the best \(100 \times (1 - \alpha)\%\) of patients as compared to an estimate of efficacy for all patients in a particular indication. The estimand for treatment efficacy in the population from which all randomized patients are drawn is the difference in counterfactual means \(E[Y_1] - E[Y_0]\), however using the trimmed means approach only the difference in trimmed means of the composite outcomes \(U_1\) and \(U_0\) are estimated. Herein, the sufficient and necessary conditions under which the trimmed means estimand and the population estimand for treatment effect are identical are formalized.

**Theorem 1.** If the outcomes among the treated and untreated are identically distributed relative to a shift and all unobserved values fall below the trim, then the treatment difference estimated by the trimmed means approach is equivalent to the treatment difference in the population, i.e.:

\[
E[U_1|U_1 > F_{U_1}^{-1}(\alpha)] - E[U_0|U_0 > F_{U_0}^{-1}(\alpha)] = E[Y_1] - E[Y_0]
\]

The proof is given in the appendix.

Theorem 1 uses the following two conditions in order to prove the equality of the trimmed means estimand and treatment difference in the whole population.
1. **Location family assumption.** The distribution of potential outcomes had the patient taken the experimental treatment \( Y_1 \sim f_1(y) \) is in the same location family as the distribution of potential outcomes had the patient taken the reference treatment \( Y_0 \sim f_0(y) \). Consider some constant \( \Delta \) then:

\[
f_0(y) = f_1(y + \Delta)
\]

2. **Strong MNAR assumption.** All missing values fall below the point at which the distributions are trimmed. Explicitly, the strong MNAR assumption states:

\[
Y_a|R_a = 0 < F_{\alpha}^{-1}(\alpha)
\]

The strong MNAR assumption ensures that the composite outcome \( U_a \) is trimmed at the same value as \( Y_a \) for all percentiles above the maximum rate of missing data between the two arms, i.e. 

\[
F_{U_a}^{-1}(\alpha) = F_{a}^{-1}(\alpha) \forall \alpha > P[R_a = 0].
\]

It also guarantees that the untrimmed distribution of \( U_a \) is identical to that of \( Y_a \).

If \( Y_1 \) and \( Y_0 \) can be identified from the observed data, then the trimmed means approach can estimate the causal estimand of treatment effect in the population given the above two assumptions as shown:

\[
E[Y_1] - E[Y_0] = E[Y_1|Y_1 > F_{1}^{-1}(\alpha)] - E[Y_0|Y_0 > F_0^{-1}(\alpha)] \tag{1}
\]

\[
= E[U_1|U_1 > F_{U_1}^{-1}(\alpha)] - E[U_0|U_0 > F_{U_0}^{-1}(\alpha)] \tag{2}
\]

\[
= E[U_1|U_1 > F_{U_1}^{-1}(\alpha), A = 1] - E[U_0|U_0 > F_{U_0}^{-1}(\alpha), A = 0]
\]

The location family assumption makes the average difference of the entire population of counterfactuals equivalent to the difference in the sub-population of counterfactuals that are not trimmed (1). The strong MNAR assumption makes the trimmed means of the counterfactuals equivalent to the trimmed means of the composite outcome (2). Then randomization and consistency allow us to identify the counterfactuals from the observed data. Note that using Theorem 1 only the difference in the counterfactual means can be recovered, albeit with a smaller sample size than if there were no MNAR data. One cannot accurately estimate the marginal means of \( Y_1 \) and \( Y_0 \) in the presence of MNAR data.

**Theorem 2.** If the difference in untrimmed means between two counterfactual distributions is equivalent to the difference in one sided trimmed means for all percentiles,

\[
E[Y_1|Y_1 > F_{1}^{-1}(\alpha)] - E[Y_0|Y_0 > F_0^{-1}(\alpha)] = E[Y_1] - E[Y_0] = \Delta \forall \alpha (0, 1)
\]

then the counterfactual distributions are a location shift of one another

\[
f_0(y) = f_1(y + \Delta)
\]

Proof is given in the appendix.

Theorem 2 demonstrates that using the trimmed means approach to estimate the population treatment effect is only relevant for treatments with an additive effect. For all possible \( \alpha \), the difference in trimmed means and the population mean are equivalent if and only if the distributions being compared are a location shift of one another. There are conditions where the difference in trimmed means and population means are equivalent when the strong MNAR assumption is not true (i.e. the MCAR case). Thus, theorem 2 reveals that the location family assumption is a sufficient and necessary condition, while the strong MNAR assumption is only a sufficient condition for the equivalence of the estimands.
3.2 Intercurrent Events

Theorem 1 extends the utility of the trimmed means approach by proving under what assumptions one can estimate the estimand representing the treatment effect based on all randomized patients rather than a subset of the best performing patients. It is important to discuss how this result fits into the estimand framework outlined in the ICH E9 addendum. The trimmed means approach is a statistical analysis that specifies how to deal with missing data, not necessarily a particular strategy to deal with intercurrent events (IE), which may often, but do not deterministically, lead to missing data. The IE strategy depends on how one handles data after observing an IE and is one of the four components in defining the estimand.

As discussed above, the trimmed means can be used as a composite approach, whereby IE that lead to missing data - and potentially others - are ranked poorly and trimmed out of the analysis. The resulting composite estimand can be thought of as a measure of treatment difference that is penalized by the amount of dropout in each arm. This penalty comes by placing the IE towards the poor end of the distribution irrespective of if the unobserved data are MAR or MNAR. In other words, they are ranked as the worst outcome even if their outcome would not have been poor had they continued in the trial. This type of estimand seems ideal for IE such as adverse events that outweigh the benefit of treatment or death. To estimate this composite estimand, the location family and strong MNAR assumptions do not need to hold. Should these assumptions be realistic however, the opportunity arises to use the trimmed means approach to estimate two other types of estimands: 1) the hypothetical and 2) intention to treat (ITT) estimands.

The hypothetical estimand postulates what would have happened had the intercurrent event not occurred and the patient remained on treatment for the duration of the trial. Even if post IE data is collected, it is discarded and treated as missing data. For the ITT estimand the IE is irrelevant, and one is interested in data that occur after the patient discontinues treatment. If this post IE data is not missing, it is used as a valid endpoint in the analysis. Both the ITT and hypothetical estimands are estimable using the trimmed means approach if the strong MNAR and location family assumptions of Theorem 1 hold. The difference between using the trimmed means approach for the hypothetical and ITT estimands is that the assumptions are made on different counterfactuals that are determined by whether or not treatment is continued post-IE. It seems more likely that the location family assumption in particular would hold for the hypothetical estimand, especially when the drug has an additive effect. The strong MNAR assumption seems more likely for the ITT estimand, but is ultimately based on the process generating the missing data. In addition, if information is collected on the reasons for missing data, and if some of these missing data can be assumed to be MAR and other strong MNAR then one could use a combination of multiple imputation and trimmed means to estimate these estimands.

4 Numerical Studies

4.1 Simulation Objectives

Numerical studies herein evaluate the finite sample properties of the trimmed means approach in estimating treatment efficacy under various missing data generating mechanisms. The simulation presented is motivated by the design of Wang et al. This earlier work is extended in a number of ways. Firstly, a comparison to MI under the various missing data generating mechanisms of the simulation is demonstrated. Additionally, when there exists a mixture of missing data types the combination approach is evaluated and compared to applying the trimmed means approach and MI globally. Furthermore, the relationship between bias and violation of the strong MNAR
assumption of theorem 1 is considered under different MNAR scenarios. Lastly, the choice of $\alpha$ is explored. The comparison of trimmed means to MI as well as the combination approach would not be possible without Theorem 1 because it demonstrates that the approaches can estimate the same estimand. Data are imputed using the mice package in R, which leverages the same methodology used by PROC MI in SAS$^{17}$.

4.2 Simulation Design

We design the study using four different ways to generate the missing data: a) Missing Completely at Random (MCAR), b) Missing at Random (MAR), c) Missing Not at Random (MNAR), and d) a mixture of all three types. Figure 1 displays the causal diagrams for these simulation designs using the $m$-graphs of Pearl$^{18}$.

![Figure 1: m-graphs for scenarios A, B, C, and D of the numerical study](image)

In these diagrams $A$ represents a binary indicator for treatment, $Y$ a continuous clinical endpoint of the study, and $R_Y$ a binary indicator variable that is equal to 1 if $Y$ is observed and 0 if $Y$ is missing. Variable $Y^*$ is the observed outcome, and its partially filled in node on the graph indicates that it has some missing values. Filled in nodes represent fully observed variables (i.e. $A$ and $R_Y$). Nodes that are not filled in represent unobserved variables (i.e. $Y$). The arrows in these graphs make explicit the assumptions about which variables have a causal effect on missingness.

We use a study sample size of $N = 100$ ($n = 50$ per treatment arm) in each of the four scenarios. Each scenario was replicated $K = 5000$ times. The $\alpha$ parameter that determines which percentile to trim in the analysis is chosen adaptively, unless stated otherwise. The upper part of the distribution is trimmed, corresponding to lower values reflecting better outcomes. The underlying model for the continuous outcome remains the same in all simulations:

$$Y = \beta_0 + \beta_A A + \epsilon$$

$Y$ is the continuous outcome variable and $A$ is the binary variable representing experimental treatment if 1 and reference treatment if 0. Here, the error term is normally distributed $\epsilon \sim N(0, \sigma^2)$. The goal is to estimate $\beta_A$, the difference of the means between treatments. In all scenarios, the values of the parameters for the outcome model are $\beta_0 = -1, \beta_A = -1, \sigma = 1.5$. We chose $\sigma = 1.5$ to obtain a benchmark ~90% power in a one-sided t-test when there is no missing data.

The missing data in outcome $Y$ were generated via the following logit model:
\[ Pr(R_Y = 1|A, Y) = \text{logit}^{-1}(\alpha_0 + \alpha_A A + \alpha_Y Y) \]

Where \( R_Y \) is the binary variable indicating that \( Y \) has been observed if equal to 1. In this model, setting parameters \( \alpha_A = \alpha_Y = 0 \) corresponds to MCAR because the missing values are unrelated to treatment or outcome. Setting parameter \( \alpha_Y = 0 \) corresponds to MAR because the missing values are only dependent on the observed values and not the unobserved outcome. If \( \alpha_Y \neq 0 \) then the model represents an MNAR missing data generating mechanism.

4.3 Simulation Results

(a) MCAR

In the MCAR setting the \( \alpha_0 \) parameter is set to values of 2.94, 2.20, 1.74, and 1.39 to induce missing data rates of 5, 10, 15, and 20 percent while keeping \( \alpha_A = \alpha_Y = 0 \). The missing data rates are the same on average in each arm since unobserved outcomes are completely random.

| Missing Rate, % | Trimmed Means |  |
|-----------------|----------------|---|
|                 | A = 1 | A = 0 | Exp | Ref | Diff (% bias) | Coverage | Power |
| 5               | 5     | 5     | -2.17 | -1.17 | -1.00 (0%) | 0.96 | 0.86 |
| 10              | 10    | 10    | -2.16 | -1.16 | -1.00 (0%) | 0.96 | 0.83 |
| 15              | 15    | 15    | -2.15 | -1.16 | -1.00 (0%) | 0.96 | 0.80 |
| 20              | 20    | 20    | -2.39 | -1.39 | -1.00 (0%) | 0.96 | 0.70 |

Table 1: Trimmed Means with MCAR

Under a completely random missing data generating mechanism (MCAR), the trimmed means approach estimates the true treatment difference without bias and with appropriate coverage even as the proportion of data missing varies (Table 1). As expected, power decreases as the amount of data not trimmed decreases. MI performed similarly in that bias and coverage were accurate (Table 2). However, as the amount of missing data increases, power does not deteriorate as quickly using MI than when using trimmed means. This is because the trimmed means approach performs inference on the subset of the observations post-trimming and thus uses a smaller effective sample size.

| Missing Rate, % | Multiple Imputation (MI) |  |
|-----------------|---------------------------|---|
|                 | A = 1 | A = 0 | Exp | Ref | Diff (% bias) | Coverage | Power |
| 5               | 5     | 5     | -2.00 | -1.00 | -1.00 (0%) | 0.94 | 0.89 |
| 10              | 10    | 10    | -2.00 | -1.00 | -1.00 (0%) | 0.94 | 0.87 |
| 15              | 15    | 15    | -1.99 | -1.00 | -0.99 (1%) | 0.94 | 0.84 |
| 20              | 20    | 20    | -1.99 | -1.01 | -0.99 (1%) | 0.94 | 0.82 |

Table 2: Multiple Imputation with MCAR
In the MAR setting, we first set the $\alpha_A$ parameter to values of -8.61, -8.27, -7.80, and -7.06 to induce missing data rates of 20, 15, 10, and 5 percent in the experimental arm while keeping $\alpha_Y = 0$ and $\alpha_0 = 10$ in order to maintain all outcomes observed in the reference arm. Next, we set $\alpha_Y = 0$ and $\alpha_A = 10$ in order to fully observe outcomes in the experimental arm while varying $\alpha_0$ to values of 2.94, 2.20, 1.73, and 1.39 to induce missing data rates of 5, 10, 15, and 20 percent in the reference arm.

As expected, the trimmed means estimator is biased in all scenarios when the missing data is truly MAR (Table 3). The bias increases when the fraction of missing data increases. The direction of the bias is positive when the reference arm has more missing data and negative when the active arm has more missing data. This directionality of the bias has an impact on power, with more MAR data in the active arm leading to a drastic decrease in power and more MAR data in the reference arm causing unreasonably high power. The trimming is directional as all missing values are placed at the poor end of each respective treatment distribution when in reality under MAR they come from all areas of the distribution. MI obtains valid estimation in this setting as it was designed explicitly for situations where data are MAR (Table 4).
Table 4: Multiple Imputation with MAR

| Missing Rate, % | Multiple Imputation (MI) |
|----------------|--------------------------|
| A = 1 | A = 0 | Exp | Ref | Diff (% bias) | Coverage | Power |
| 20 | 0 | -1.99 | -1.00 | -0.99 (-1%) | 0.94 | 0.86 |
| 15 | 0 | -2.00 | -1.00 | -1.00 (0%) | 0.94 | 0.88 |
| 10 | 0 | -2.00 | -1.00 | -1.00 (0%) | 0.95 | 0.89 |
| 5 | 0 | -1.99 | -1.00 | -1.00 (0%) | 0.95 | 0.91 |
| 0 | 5 | -2.00 | -1.00 | -1.00 (0%) | 0.94 | 0.90 |
| 0 | 10 | -2.00 | -1.00 | -1.00 (0%) | 0.95 | 0.90 |
| 0 | 15 | -2.00 | -1.01 | -1.00 (0%) | 0.95 | 0.88 |
| 0 | 20 | -2.00 | -1.01 | -1.00 (0%) | 0.94 | 0.86 |

(c) MNAR

In the MNAR setting, the $\alpha_Y$ parameter was set to values of -1, -2.5, -5, and -10 causing higher values of $Y$ to be more likely to be missing while keeping $\alpha_0 = 2.85$ and $\alpha_A = 0$. Here, $\alpha_Y$ is negative because a decrease in $Y$ reflects a better outcome. This setup induces missing data rates in the experimental vs reference arms of 2 vs 5, 3 vs 10, 5 vs 15, and 7 vs 20 respectively. The missing data are not simulated strictly as strong MNAR but a general MNAR missing data mechanism.

Table 5: Trimmed Means with MNAR

| Missing Rate, % | Trimmed Means |
|----------------|---------------|
| A = 1 | A = 0 | Exp | Ref | Diff (% bias) | Coverage | Power |
| 2 | 5 | -2.14 | -1.11 | -1.04 (-4%) | 0.96 | 0.90 |
| 3 | 10 | -2.28 | -1.26 | -1.02 (-2%) | 0.96 | 0.90 |
| 5 | 15 | -2.41 | -1.41 | -1.00 (0%) | 0.96 | 0.90 |
| 7 | 20 | -2.51 | -1.51 | -1.00 (0%) | 0.95 | 0.89 |

The trimmed means approach is fairly unbiased, obtains ideal coverage, and maintains its power in the MNAR setup as the amount of missing data increases (Table 5). While the marginal means in each arm are biased, the means in each arm increase at equal rates and keep the estimate of their difference unbiased. Multiple imputation increases bias, reduces coverage of the true effect, and loses power as the fraction of MNAR data increases (Table 6).
(d) Mixture: MCAR, MAR, and MNAR

Having a mixture of reasons for missing data reflects the information one would have in a closely monitored clinical trial. In many trials, data are missing for a combination of reasons such as lack of efficacy, intolerability, and administrative reasons. In order to generate such data the deletion strategies used in the previous three sections are combined. MNAR data (R3) were deleted first at rates of 2 vs 5, 3 vs 10, 5 vs 15, and 7 vs 20 in the experimental vs reference arms respectively. MAR data (R2) were then generated in the experimental group at rates of 23, 17, 10, and 3. MCAR data (R1) were generated at a rate of 5 percent in each arm. Overall, the missing data rates in the four mixture scenarios in the experimental vs reference arms are 10 vs 30, 15 vs 25, 20 vs 20, and 15 vs 25 respectively.

In the mixture setting, the performance of trimmed means applied globally is directly related to the proportion of MAR missing data (Table 7). This fraction of MAR data decreases across the four scenarios and consequently bias, coverage, and power improve across the scenarios. Contrarily, MI applied globally performs well with a large fraction of MAR data and its performance weakens as the proportion of MNAR data increases (Table 8). The combination of trimmed means and MI exhibits improved bias, coverage, and power as compared to each method applied individually (Table 9). Bias is at most 3%, no matter the variation in the fraction of missing data due to MAR and MNAR. Coverage and Power are near the optimal 0.95 and 0.90.
### Multiple Imputation (MI)

| Trt | R1 | R2 | R3 | Overall | Exp | Ref | Diff (% bias) | Coverage | Power |
|-----|----|----|----|---------|-----|-----|--------------|----------|-------|
| $A = 1$ | 5  | 23 | 2  | 30      | -2.04 | -1.13 | -0.91 (9%)   | 0.92     | 0.79  |
| $A = 0$ | 5  | 0  | 5  | 10      |       |     |              |          |       |
| $A = 1$ | 5  | 17 | 3  | 25      | -2.10 | -1.31 | -0.79 (21%)  | 0.87     | 0.73  |
| $A = 0$ | 5  | 0  | 10 | 15      |       |     |              |          |       |
| $A = 1$ | 5  | 10 | 5  | 20      | -2.14 | -1.41 | -0.73 (27%)  | 0.83     | 0.70  |
| $A = 0$ | 5  | 0  | 15 | 20      |       |     |              |          |       |
| $A = 1$ | 5  | 3  | 7  | 15      | -2.20 | -1.54 | -0.66 (34%)  | 0.75     | 0.66  |
| $A = 0$ | 5  | 0  | 20 | 25      |       |     |              |          |       |

Table 8: Multiple Imputation with a Mixture of Missing Data Types

### Trimmed Means + MI

| Trt | R1 | R2 | R3 | Overall | Exp | Ref | Diff (% bias) | Coverage | Power |
|-----|----|----|----|---------|-----|-----|--------------|----------|-------|
| $A = 1$ | 5  | 23 | 2  | 30      | -2.17 | -1.14 | -1.03 (-3%)  | 0.92     | 0.88  |
| $A = 0$ | 5  | 0  | 5  | 10      |       |     |              |          |       |
| $A = 1$ | 5  | 17 | 3  | 25      | -2.32 | -1.31 | -1.01 (-1%)  | 0.93     | 0.88  |
| $A = 0$ | 5  | 0  | 10 | 15      |       |     |              |          |       |
| $A = 1$ | 5  | 10 | 5  | 20      | -2.42 | -1.42 | -1.00 (-0%)  | 0.94     | 0.88  |
| $A = 0$ | 5  | 0  | 15 | 20      |       |     |              |          |       |
| $A = 1$ | 5  | 3  | 7  | 15      | -2.53 | -1.54 | -0.99 (1%)   | 0.94     | 0.89  |
| $A = 0$ | 5  | 0  | 20 | 25      |       |     |              |          |       |

Table 9: Trimmed Means + MI with a Mixture of Missing Data Types

**(e) Choice of $\alpha$ and Strong MNAR Assumption**

The analyst chooses $\alpha$, the proportion trimmed from each treatment arm – which can be set to any value above the maximum proportion of missing data between the two arms. For all previous simulations the value of $\alpha$ was chosen adaptively. Herein, the adaptive choice of $\alpha$ is compared to a fixed choice where $\alpha = 0.5$. In addition, to investigate the strong MNAR assumption of Theorem 1, the percent of missing values that would have fallen below the trim point had they been observed is calculated for each scenario. The adaptive and fixed $\alpha$ approaches are evaluated under 10 different MNAR data generating mechanisms using the same logit model as before. The $\alpha_Y$ parameter was set to values of -0.5, -1, -1.5, -2, -2.5, -3, -4, -5, -7.5 and -10 while keeping $\alpha_0 = 2.85$ and $\alpha_A = 0$. Rates of missing data and results are shown in Table 10.
Overall, both the fixed and adaptive $\alpha$ accurately estimate the true difference in treatment effects ($\beta_A = -1$). As $\alpha_Y$ moves further from 0, the percentage of missing values falling below the trim point (i.e. sMNAR) increases. As a consequence, bias decreases which is consistent with the theoretical result of Theorem 1. Unlike in imputation, bias when using trimmed means is not directly related to the fraction of missing data, but rather due to sMNAR. Thus, it is possible to observe lower bias despite larger amounts of missing data, as is demonstrated here. The fixed $\alpha$ approach consistently has a higher sMNAR than the adaptive approach. This explains why using the fixed $\alpha$ has lower bias in all scenarios: the underlying missing values have a higher likelihood of falling below the more extreme trimming quantile. Using the adaptive $\alpha$ has a smaller variance than the fixed $\alpha$ because the adaptive approach trims the least amount of data possible. The smaller variance of the adaptive approach translated to a smaller MSE than the fixed approach despite the fixed approach having less bias. This simulation highlights the bias vs variance tradeoff associated with increasing the percentage of data trimmed.

## 5 Application to a Clinical Trial

We applied the methodologies described above to data from a double-blind randomized clinical trial of two treatments (A and B) conducted in patients with neuropathic pain due to diabetic neuropathy. Seventy-one patients were randomized to treatment A and seventy to treatment B. The outcome of interest was change in pain severity from baseline to week 16, as assessed on a Visual Analog Scale (VAS). VAS is a well-studied instrument for recording pain where a score of 100 reflects the “worst pain possible” and a score of 0 reflects “no pain”\(^{19}\). Pain scores were recorded in a digital diary daily by patients. At most, there were 16 weekly pain measurements for each patient, produced by averaging daily pain recordings during each week.
Study discontinuation in this clinical trial was common, as there were 53 (38%) patients who did not stay on trial for 16 weeks. Discontinuation differed among treatment arms, 33 (46%) in the treatment A arm and 20 (29%) in the treatment B arm. The reason for discontinuing the study was recorded for each dropout and categorized as Adverse Event (AE), Loss of Efficacy (LoE), or Administrative (Table 11). The rates of study discontinuation, the time at which they occurred, and the observed data before dropout were used to inform missing data assumptions. AE and LoE generally occurred during the first half of the study period while administrative dropout occurred uniformly throughout the trial. On average AE and LoE occurred after 6.77 and 6.83 weeks on trial, respectively, and administrative dropouts after 10.6 weeks. Based on this exploratory data analysis and our clinical knowledge, we assume that the dropouts classified as AE & LoE were MNAR and administrative dropouts were MCAR.

We applied 5 different methods to the trial data. First, the trimmed means approach was applied globally to all dropouts (i.e. assumes all dropouts MNAR). The fraction trimmed was chosen adaptively and thus corresponded to the amount of dropout in the treatment A arm (i.e. $\alpha = 0.46$). To test the location shift assumption, we performed a Kolmogorov-Smirnov test between the distribution of trt A shifted by the treatment effect compared to the observed distribution of treatment B. The test failed to reject that the untrimmed outcome distributions were a location shift of one another ($D = 0.0946, p = 0.9849$). We also applied multiple imputation to all dropouts in an ANOVA model despite the MAR assumption being unlikely for many dropouts. Next, we applied the approach that combines trimmed means and multiple imputation. To do this, we trimmed AE and LoE (MNAR) and imputed administrative dropout data (MCAR). As a consequence, the fraction trimmed was reduced to $\alpha = 0.30$ in each of the imputed datasets. Lastly, we applied two more approaches for historical reference, a complete case analysis of all patients completing the trial (i.e. assumes all dropouts MCAR) and a Last Observation Carried Forward (LOCF) analysis.

| Method                     | Pain Difference | SE   | 95% CI          | $p$-value |
|----------------------------|-----------------|------|-----------------|-----------|
| Trimmed Means              | -14.48          | 7.61 | [-29.38, 0.43] | 0.055     |
| Trimmed Means + MI        | -12.67          | 6.21 | [-24.83, -0.49] | 0.041     |
| Complete Case Analysis    | -3.74           | 5.39 | [-14.45, 6.97]  | 0.497     |
| Multiple Imputation       | -2.71           | 4.68 | [-11.88, 6.45]  | 0.537     |
| LOCF                      | -1.76           | 4.20 | [-10.06, 6.54]  | 0.675     |

Table 12: Clinical Trial Analysis Results

Table 12 contains the results of each of these approaches. The trimmed means applied to all
dropouts showed the largest treatment difference of -14.48 points lower on the pain VAS; however, the trimming inflated the standard error to 7.61. Similarly, the combination of trimmed means and MI had the second largest effect size -12.67. Contrarily, the combination approach trimmed less data which resulted in a less inflated standard error. These two methods, which involve trimming, resulted in a larger effect size than the other methods because they allow for the fact that the worse performing treatment had a higher dropout rate. The other approaches presented are not appropriate given our missing data assumptions, but were included for illustrative purposes as a reference, especially the relative standard errors.

Focusing on the SE column, we see that LOCF has the smallest standard error, 4.20, as expected since the method does not admit to missing data; it replaces all missing data with the last available data point, in time, for each patient based on a single imputation. Some object to this method being unrealistic in this situation. The next smallest entry, 4.68, Multiple Imputation, treats all missing data as missing at random, which may not be plausible for all discontinuation reasons in this trial. Once again, the method creates data whenever they are missing, except not once, as in LOCF, but multiple times in order to better reflect the uncertainty induced by the missing data. The complete case analysis has the next smallest value, 5.39. This was only included for completeness. In general, the shortcomings of this method are well known. The next smallest is the Trimmed Means + MI, 6.21. This approach achieves an unbiased comparison by maintaining an “equal percentage” of the data for those who prematurely leave the study for cause. This method also permits distinguishing between observations that are truly missing at random and other observations for which the missing at random assumption is not plausible (i.e. missing not at random). The last one, the Trimmed Mean method has the largest standard error, 7.61. This is easily explained because this is the method that discards the most data. This is excessive in that the fraction of the missing data that are missing at random are best handled as missing at random and thus amenable to multiple imputation.

6 Discussion

Our work extends the utility of the trimmed means approach for missing data in two key ways: 1) It determines sufficient conditions for which the trimmed means approach can identify the estimand for the population treatment effect; and 2) It demonstrates that when different types of missing data are present and can be distinguished, one could combine the trimmed means approach with multiple imputation to improve estimation.

The trimmed means approach was originally designed to estimate a unique estimand: the treatment difference in the best (100 × α) % of patients of each arm. The work herein allows us to view the trimmed means approach in a different way, not a method estimating a unique estimand, but a method that targets the usual estimand of a clinical trial where accuracy depends on how well the assumptions are satisfied.

Missing data inferences are not possible without assumptions. The strong MNAR assumption, similar to the MAR assumption, is untestable. It is a conservative assumption that assumes every missing value falls below the trimming quantile. It would be rare for this assumption to hold perfectly; however, when applied to dropouts reporting loss of efficacy, where poor outcomes are the primary cause of dropout, the assumption may hold for enough of the missing data to justify adopting the trimmed means approach. Also the numerical studies show that the trimmed means estimator can still perform well under MNAR scenarios that are not explicitly strong MNAR. Thus, the assumption may be robust to slight deviations. One interesting paradox is that while trimming more data leads to a loss in efficiency, theoretically it allows the strong MNAR assumption
to become more plausible since missing values are then more likely to be trimmed. The simulation comparing a fixed to adaptive choice of $\alpha$ demonstrates this. This bias/variance trade off should be considered when choosing the value of $\alpha$. The location shift assumption may be more realistic, is testable among the observed values, and is often assumed in many statistical methods. In practice, the untrimmed fractions of the distributions for each treatment arm of the study should be compared using a Kolmogorov-Smirnov test to assess the validity of this assumption. Of course should neither the location family nor the strong MNAR assumptions be plausible, the trimmed means approach can still be useful in estimating the original composite estimand in the sub-population of the trial for which it was originally developed.

This research highlights the importance for administrators and physicians conducting clinical trials to document the reasons for dropout. If close collaboration between statisticians and clinicians can inform which dropouts are MCAR, MAR, or MNAR then analysts may have a combination of data that can be imputable and other data that should be trimmed away using the trimmed means approach. This combination approach can protect analysts from penalizing themselves using trimmed means globally for all missing data but also respects the assumption that patients may drop out of the trial due to poor health outcomes. If a fraction of dropouts are missing because of factors unrelated to their unobserved outcomes (MAR), the bias and loss of power using trimmed means for all dropouts can be drastic. Choosing which missing data to treat as MAR or MNAR will vary from trial to trial, and will also be dependent on the particular estimand of interest. Clinical input is crucial for the mixture approach to be effective. One limitation of the combination approach is that MNAR dropouts must precede MAR dropouts; otherwise the complete cases leveraged for imputations may have a different outcome distribution than the MAR outcomes.

The clinical trial example highlights the importance of combining trimmed means and multiple imputation. MCAR data is by definition evenly distributed between each arm of the study; therefore, it does not cause bias when applying trimmed means. However, there is considerable power loss as shown in MCAR situation of our simulations (section 4a). In the clinical trial analysis, applying trimmed means to all dropouts produced a larger estimate of the difference in treatment effects, but because 46% of observations were missing in one arm of the study the standard errors were inflated, making it harder to reject the null hypothesis of no difference between treatments. The combination approach, however, preserved a similar estimate of the treatment comparison and did not inflate standard errors as drastically. The combination approach leverages a larger effective sample size than applying trimmed means alone.

The trimmed means approach is a creative solution to estimating treatment effects in a clinical trial when missing data can safely be assumed to be due to poor outcomes. As is the case in any missing data analysis, especially those with MNAR data, no analytical method replaces a good sensitivity analysis to determine the plausible range of what could have happened. While no method can fully or confidently rectify the issues caused by missing data, a combination of multiple imputation and/or trimmed means could be useful when the assumptions of both methods are satisfied.

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Appendix: Proofs

Proof of Theorem 1.

Consider counterfactuals $Y_1$ and $Y_0$ with absolutely continuous distribution functions $f_1(y)$ and $f_0(y)$ respectively both defined over a common domain $(-\infty, \infty)$. Here, $R_a$ is a binary indicator of $Y_a$ being observed or missing. Here, binary treatment $a \in \{0, 1\}$ determines which of the two counterfactuals is observed and is intervened on through randomization. Lastly consider the transformation of counterfactual $Y_a$ such that:

$$U_a = \begin{cases} Y_a & \text{if } R_a = 1 \\ \min(Y_a|R_a = 1) - \epsilon & \text{if } R_a = 0 \end{cases}$$

for $\epsilon > 0$.

There exist two sufficient conditions in order to prove the equality of the trimmed means estimand and treatment difference in the whole population. The first condition – the location family assumption - is that the distribution of potential outcomes from the experimental group $Y_1 \sim f_1(y)$ is in the same location family as the distribution of potential outcomes from the reference group $Y_0 \sim f_0(y)$. Consider some constant $\Delta$ then $f_0(y) = \Delta$ if two distributions are a location shift of one another then $E[Y_1] = E[Y_0] + \Delta$ because the mean is the location parameter of a distribution. Also, note that as a consequence all quantiles of these distributions are a location shift of one another i.e. $F_0^{-1}(a) + \Delta = F_1^{-1}(a)$. The second condition – strong MNAR assumption - is that all missing values fall below the point at which the distributions are trimmed, i.e. $Y_a|R_a = 0 < F_0^{-1}(\alpha)$. The strong MNAR assumption ensures that the composite outcome $U_a$ is trimmed at the same value as $Y_a$ for all percentiles above the maximum rate of missing data between the two arms, i.e. $F_U^{-1}(\alpha) = F_0^{-1}(\alpha) \forall \alpha > Pr[R_a = 0]$. Leveraging both assumptions we can demonstrate the equality of the two estimands:

$$E[U_1|U_1 > F_U^{-1}(\alpha)] - E[U_0|U_0 > F_U^{-1}(\alpha)] = E[Y_1|Y_1 > F_1^{-1}(\alpha)] - E[Y_0|Y_0 > F_0^{-1}(\alpha)]$$

$$= \frac{1}{1 - \alpha} \int_{F_1^{-1}(\alpha)}^{\infty} y f_1(y) dy - \frac{1}{1 - \alpha} \int_{F_0^{-1}(\alpha)}^{\infty} y f_0(y) dy$$

$$= \frac{1}{1 - \alpha} \left[ \int_{F_1^{-1}(\alpha)}^{\infty} y f_1(y) dy - \int_{F_0^{-1}(\alpha)}^{\infty} y f_0(y) dy \right]$$

$$= \frac{1}{1 - \alpha} \left[ \int_{F_1^{-1}(\alpha)}^{\infty} y f_1(y) dy - \int_{F_0^{-1}(\alpha)}^{\infty} y f_1(y + \Delta) dy \right]$$

$$= \frac{1}{1 - \alpha} \left[ \int_{F_1^{-1}(\alpha)}^{\infty} y f_1(y) dy - \int_{F_1^{-1}(\alpha)}^{\infty} (x - \Delta) f_1(x) dx \right] \quad x = y + \Delta$$

$$= \frac{1}{1 - \alpha} \left[ \int_{F_1^{-1}(\alpha)}^{\infty} y f_1(y) dy - \int_{F_1^{-1}(\alpha)}^{\infty} x f_1(x) dx + \int_{F_1^{-1}(\alpha)}^{\infty} f_1(x) dx \right]$$

$$= \frac{1}{1 - \alpha} \left[ \Delta \int_{F_1^{-1}(\alpha)}^{\infty} f_1(x) dx \right]$$

$$= \frac{1}{1 - \alpha} [\Delta [1 - \alpha]]$$

$$= \Delta$$
= E[Y_0] - E[Y_0] + \Delta
= E[Y_1] - E[Y_0]

Which completes the proof.

**Proof of Theorem 2.**

Consider two distributions \( F_1(\cdot) \) and \( F_0(\cdot) \) which are absolutely continuous distribution functions defined over a common domain \((-\infty, \infty)\). Also, both distributions have an expectation and that expectation is finite. Assume that the differences between the \( \alpha \)-trimmed means are the same constant \( \Delta \in \mathbb{R} \) for all \( \alpha \in [0, 1] \) that is:

\[
E[Y_1|Y_1 > F_1^{-1}(\alpha)] - \frac{\alpha}{1-\alpha} \int_{F_0^{-1}(\alpha)}^{\infty} y f_0(y) dy = \Delta - \frac{\alpha}{1-\alpha} \int_{F_1^{-1}(\alpha)}^{\infty} y f_1(y) dy
\]

At this stage perform the substitution of \( y = F_0^{-1}(\beta) \), \( d\beta = f_0(y) dy \) for the integral on the left side of the equation and \( x = F_1^{-1}(\beta) - \Delta, \ d\beta = f(x + \Delta) dx \) for the integral on the right side of the equation such that:

\[
\int_{\alpha}^{1} F_0^{-1}(\beta) d\beta = \int_{\alpha}^{1} [F_1^{-1}(\beta) - \Delta] d\beta
\]

\[
\frac{d}{d\alpha} \int_{\alpha}^{1} F_0^{-1}(\beta) d\beta = \frac{d}{d\alpha} \int_{\alpha}^{1} [F_1^{-1}(\beta) - \Delta] d\beta
\]

\[
\int_{\alpha}^{1} F_0^{-1}(\beta) d\beta = \int_{\alpha}^{1} F_1^{-1}(\beta) - \Delta d\beta
\]

\[
-\frac{\alpha}{1-\alpha} \int_{F_0^{-1}(\alpha)}^{\infty} y f_0(y) dy = \frac{\alpha}{1-\alpha} \int_{F_1^{-1}(\alpha)}^{\infty} y f_1(y) dy
\]

From here it follows that \( F_1 - \Delta = F_0 \) and it is proven that \( F_1 \) is a location shift of \( F_0 \) almost everywhere on the domain i.e. \( f_0(y) = f_1(y + \Delta) \).