Paper AS07

# Advancing Clinical Trial Analysis with Trimmed Means: Estimands, Intercurrent Events, and Regulatory Alignment

Prasanth Palanisamy, SENSAN Biosciences, Chennai, India

## ABSTRACT

This presentation provides a detailed analysis of trimmed means, particularly addressing ICEs (Intercurrent Events) within the framework established by the ICH E9(R1) addendum. Based on Permutt and Li approach is highly related to handling the ICEs such as treatment discontinuation due to lack of efficacy or the occurrence of severe adverse events.

This particular use of trimmed means basically redefines the "missing data problem." As an alternative of looking, it solely as a statistical imputation challenge, it treats dropout as a clinical outcome. This approach efficiently treats these events as "bad outcomes", that are then accounted for by trimming them from the analysis with one-sided trimming method is particularly suited for Missing Not At Random (MNAR) scenarios.

FDA recognizes estimands framework and robust statistical techniques. Trimmed means are currently more commonly used for sensitivity analyses than as primary efficacy endpoints. This presentation outlines calculation, assumptions, and application through SAS.

## INTRODUCTION

This paper examines the use of trimmed means as a robust statistical method increasingly recognized in clinical trial analysis, particularly for addressing intercurrent events (ICEs) within the ICH E9(R1) estimand framework. By down-weighting or excluding extreme outcomes and data affected by non-random missingness, trimmed means provide a stable estimate of treatment effect for a clearly defined sub-population, offering a principled alternative to traditional imputation-based approaches.

The Permutt and Li trimmed mean approach is especially relevant for ICEs such as treatment discontinuation due to lack of efficacy or severe adverse events, which are implicitly treated as poor outcomes and accommodated through trimming. This method defines an estimand targeting patients who do not experience extreme negative outcomes. While regulators acknowledge robust methods and estimand-based analyses, publicly available examples of approvals relying on trimmed means as a primary endpoint are limited, suggesting their current role is more common in sensitivity analyses or in narrowly justified primary estimands.

## INTRODUCTION TO TRIMMED MEANS

### A. DEFINITION AND CONCEPTUAL BASIS OF TRIMMED MEANS

A trimmed mean (or truncated mean) is a measure of central tendency calculated after removing a pre-specified proportion of the largest and smallest values from a dataset. By reducing the influence of extreme or a typical observation, this approach provides a more robust and representative estimate of the central tendency than the arithmetic mean. Conceptually, trimming reflects a deliberate focus on the central portion of the distribution, redefining the “average” to better represent the bulk of the data, particularly when tail values are highly variable or driven by uncommon events.

### B. ADVANTAGES OF TRIMMED MEANS IN HANDLING OUTLIERS AND SKEWED DATA

Trimmed means are considered robust measures of central tendency because they are less affected by outliers, skewed data, or departures from ideal statistical assumptions than the ordinary mean. By removing extreme values, trimmed means provide more stable and reliable results, especially when data are not normally distributed or show large variability on one side. This can also lead to more consistent standard errors and, in some situations, improved statistical power compared with traditional methods.

Beyond statistical advantages, trimmed means can support a more clinically meaningful interpretation of treatment effects. In diverse patient populations, extreme outcomes such as severe adverse events or rapid disease worsening may mask the treatment effect seen in most patients. Trimming these values allows the analysis to focus on the majority of participants. While this approach may slightly reduce statistical efficiency compared with ideal methods under perfect assumptions, it offers a practical balance between robustness and interpretability, particularly when data are complex or influenced by real-world factors.

#### C. COMPARISON WITH TRADITIONAL MEASURES OF CENTRAL TENDENCY (MEAN, MEDIAN)

Choosing between the mean, median, and trimmed mean is not just a technical decision. It reflects what treatment effect you want to estimate and what clinical question you are trying to answer. Each measure summarizes the data differently and therefore targets a different estimand.

The mean uses all values and represents the average outcome, but it is very sensitive to extreme values and can be misleading when data are skewed or contain outliers. The median gives the middle value and is highly resistant to extremes, but it ignores much of the information in the data. The trimmed mean sits between these two approaches: it removes only a small proportion of extreme values, keeping more information than the median while being more robust than the mean. This allows a balanced and clinically meaningful definition of the “average” treatment effect, consistent with the ICH E9(R1) emphasis on clearly defining the estimand before choosing the analysis method.

## INTERCURRENT EVENTS AND THE ICH E9(R1) ESTIMAND FRAMEWORK

#### A. UNDERSTANDING INTERCURRENT EVENTS (ICES) IN CLINICAL TRIALS

Intercurrent events (ICEs) are defined as events occurring after treatment initiation (or post-randomization in randomized trials) that affect either the interpretation or the very existence of outcome data. These events are distinct from simple missing values due to study withdrawal or loss to follow-up, which are considered data limitations rather than intercurrent events that inherently alter the clinical question.

Examples of ICEs frequently encountered in clinical trials include:

- **Use of alternative treatment:** Such as the administration of rescue medication.
- **Discontinuation of assigned treatment:** Patients may stop taking the study drug early.
- **Terminal events:** Such as death.

ICEs are broadly categorized into two types:

**Treatment-modifying events:** These events influence the receipt of the assigned treatment. For instance, early discontinuation of a drug or the use of rescue treatment in an asthma study would be treatment-modifying ICEs. These events affect the interpretation of outcome data because outcomes from participants who experienced the event might provide different information about the treatment than outcomes from those who did not.

**Truncating events:** These events prevent the existence of the outcome data. Death is the most common example, often referred to as truncation by death. If a patient dies, subsequent outcome measurements cannot exist. Other examples include limb amputation when the outcome is a symptom score for that limb, or miscarriage when the outcome is neonatal birth weight. In time-to-event studies, truncating events that preclude the outcome of interest are often termed competing events.

The precise definition and categorization of ICEs are critical because different types of ICEs necessitate different strategies within the estimand framework, directly influencing the interpretation of treatment effects. Misclassifying an event for example, treating an ICE as simple missing data can lead to inappropriate statistical methods and potentially biased conclusions. This underscores the importance of multidisciplinary discussion involving clinicians, statisticians, and regulators during the trial planning phase to accurately define ICEs and their intended handling.

#### B. OVERVIEW OF THE ICH E9(R1) ESTIMAND FRAMEWORK AND ITS ATTRIBUTES

The ICH E9(R1) addendum introduces a structured framework for defining estimands, which are precise descriptions of the treatment effect that align with the clinical question posed by a given clinical trial objective. An estimand clarifies "what to estimate" and serves to align trial objectives with its design, data collection, and statistical analysis methods.

This framework expands upon the widely used PICO (Population, Intervention, Comparator, Outcome) framework by incorporating two additional, crucial attributes:

**Summary measure:** This defines how outcomes are summarized and compared between treatment groups.

**Strategies for handling each type of intercurrent event:** This specifies how ICEs will be addressed in the definition of the treatment effect.

The ICH E9(R1) outlines five distinct strategies for handling ICEs, each reflecting a different clinical question or interpretation of the treatment effect:

**Treatment Policy Strategy:** The occurrence of the ICE is considered part of the treatment condition, and outcomes are used regardless of whether the event occurred. This strategy is useful for evaluating the effect of an intervention as it would be used in routine practice, including any associated discontinuations.

**Hypothetical Strategy:** This strategy evaluates the treatment effect in a hypothetical scenario where the observed ICE would not have occurred. It often involves excluding data after the ICE and using statistical methods to estimate potential outcomes in an uninterrupted scenario.

**Composite Strategy:** The occurrence of the ICE is incorporated directly into the endpoint definition, often by assigning a specific value to participants who experience the event.

**While on Treatment Strategy:** Only measurements collected before and at the time of the ICE are considered, focusing on the treatment effect prior to the event.

**Principal Stratum Strategy:** The population of interest is defined based on whether an ICE would or would not occur on a particular treatment arm, and the treatment effect is estimated exclusively within this defined stratum. The estimand framework represents a fundamental shift in clinical trial design and analysis, moving from a sole focus on statistical methods to a more holistic, clinically driven definition of the treatment effect.

This approach enhances transparency and reduces ambiguity in interpreting trial results, particularly in the presence of complex patient pathways and events. By requiring explicit consideration of how ICEs impact the clinical question before data analysis, the framework leads to more robust and interpretable results that directly address the trial's objective.

This proactive approach minimizes the need for post-hoc justifications for handling complex data, and regulatory bodies increasingly expect this level of clarity in trial protocols and statistical analysis plans.

#### C. THE COMPOSITE STRATEGY FOR HANDLING INTERCURRENT EVENTS

With a composite strategy, an intercurrent event (ICE) is built directly into the study outcome. This means that if a patient experiences an ICE, they are given a predefined outcome value, and this value becomes part of the endpoint used in the analysis. By doing this, the endpoint itself is changed, which also changes the estimand.

For example, in an asthma trial, patients who stop treatment early could be assigned a fixed lung function value, such as an FEV1 of 60% or 50%. Choosing 60% versus 50% leads to different estimands, because each choice reflects a different clinical interpretation of what treatment discontinuation means.

The composite strategy is especially useful for truncating events, such as death, because it ensures these events are treated as negative outcomes. For instance, defining the endpoint as “days alive without a ventilator” makes sure that death is not mistakenly counted as a good outcome in a study where fewer ventilator days would otherwise look beneficial.

Although the composite strategy clearly defines what is being estimated, it can be hard to interpret when the composite endpoint includes events with very different clinical importance, such as a mild adverse event and death. Because of this, the value assigned to the intercurrent event is extremely important and must make clinical sense.

The chosen value directly affects both the size and meaning of the treatment effect. If the value is poorly chosen, the estimand may be statistically correct but clinically confusing or misleading. For example, assigning a “moderately abnormal” value to death would not make clinical sense. This shows why strong clinical input is essential when defining composite estimands, so that the assigned values truly reflect how serious the intercurrent event is.

**TABLE 1: COMPARISON OF INTERCURRENT EVENT HANDLING STRATEGIES (ICH E9(R1))**

| Strategy Name | Definition | Key Consideration/Implication |
|---|---|---|
| Treatment Policy | The occurrence of the ICE is considered part of the treatment condition; outcomes are used regardless of the ICE. | Evaluates the effect of an intervention as used in routine practice, including associated discontinuations. It cannot be used for truncating events as it requires outcome data after the event. |
| Hypothetical | Evaluates the treatment effect in a fictitious scenario where the ICE would not have occurred. | Excludes data after ICEs and uses statistical methods to estimate potential outcomes in an uninterrupted scenario. |
| Composite | The occurrence of the ICE is integrated into the endpoint definition, often by assigning a | Modifies the endpoint attribute of the estimand. Useful for ensuring truncating events are reflected as |

| | | |
|---|---|---|
| | specific value to participants who experience the event. | undesirable outcomes. Requires careful clinical justification for assigned values. |
| While on Treatment | Focuses on measurements before and at the time of the ICE, considering only the treatment effect prior to the event. | Relevant when the effect of interest is strictly during active treatment exposure. |
| Principal Stratum | Defines the population of interest based on whether an ICE would or would not occur on a particular treatment arm, estimating the effect exclusively within this stratum. | Addresses a specific subpopulation, often requiring complex statistical methods and strong assumptions about counterfactuals. |

## APPLICATION OF TRIMMED MEANS IN CLINICAL TRIALS FOR INTERCURRENT EVENTS

### A. TRIMMED MEANS AS A ROBUST APPROACH FOR MISSING DATA (E.G., DROPOUT)

The trimmed means approach, developed by Li and Permutt, is designed for situations where missing data, especially from patients dropping out, are likely due to poor health or treatment intolerance. In other words, the missing data is not random (MNAR). Patients often leave trials because their condition is not improving or they cannot tolerate the treatment. If we only analyze the patients who finish the trial, the results will likely overestimate the treatment's effectiveness, because the data from completers are generally better than the data from everyone who started the trial.

To handle this, the trimmed means approach assigns missing values (from dropouts) the worst observed outcome or a value slightly worse than the poorest outcome in that treatment group. Then, a fraction of the lowest outcomes is trimmed from each group before calculating the treatment effect. This trimming also implicitly rewards treatment arms with fewer dropouts, recognizing that lower dropout is a positive effect of the drug, while higher dropout indicates a negative outcome.

Unlike traditional methods that try to guess or impute missing values, the trimmed means approach treats dropout as a meaningful, undesirable outcome. By assigning dropouts to the worst outcomes and trimming them, the method estimates the treatment effect among those who tolerated the treatment or responded to it. This produces a clinically relevant estimand that focuses on the "responder" subgroup, capturing treatment effects in a way that reflects real-world dropout patterns, rather than relying on assumptions about what missing values might have been.

### B. INTEGRATING TRIMMED MEANS WITH THE COMPOSITE STRATEGY FOR ICES

The trimmed means approach works well with the composite strategy from ICH E9(R1) because it directly includes intercurrent events (ICEs), like treatment discontinuation, in the endpoint. Patients who experience these events are assigned a "worst outcome" value, which ensures that their data are considered among the poorest before being trimmed from the analysis. The exact number assigned isn't critical, as long as it is low enough to rank among the worst outcomes. This method is especially useful for longitudinal measurements collected at multiple time points, such as visual acuity in eye trials, where missing data due to ICEs can be treated as a meaningful outcome itself.

By combining trimmed means with the composite strategy, researchers can create a clear and interpretable estimand that reflects the effect of treatment on patients who continue therapy or respond well. At the same time, it conservatively accounts for patients who drop out or fail treatment. Essentially, trimming automatically implements the composite strategy: the worst outcomes (dropouts or failures) are removed, and the remaining data represent the effect on the "better outcome" patients, providing a robust measure of treatment success or tolerability.

### C. SCENARIOS WHERE TRIMMED MEANS ARE PARTICULARLY APPLICABLE (E.G., MNAR DATA)

The trimmed means approach works best in specific situations and is not a one-size-fits-all solution for missing data. Its main advantage is in handling Missing Not At Random (MNAR) cases, where the reason a value is missing gives meaningful information about a poor outcome. In such cases, the method links the statistical analysis directly to a clinical interpretation, making it more relevant than standard methods.

Trimmed means are especially useful for datasets that are highly variable or very skewed. They work well when missing data are strongly related to negative outcomes, such as patients dropping out because the treatment is ineffective or causes severe side effects. The method can also be applied to other intercurrent events, like switching to rescue medication, which also signals a poor outcome.

However, trimmed means are not suitable for data that are Missing At Random (MAR), where missingness is unrelated to outcomes. In those cases, methods like multiple imputation are better. Using trimmed means requires a clear understanding of why data are missing and a strong clinical or biological reason to assume missing points are "bad outcomes." This aligns with the ICH E9(R1) guidance, which emphasizes clearly defining the estimand and how intercurrent events are handled, since the method's appropriateness depends entirely on these definitions.

## STATISTICAL METHODOLOGY OF TRIMMED MEANS

### A. DETAILED CALCULATION OF TRIMMED MEANS AND TRIMMING PERCENTAGES

The calculation of a trimmed mean involves a systematic process to remove extreme values before computing the average.

The steps are as follows:

1. **Order Data:** All observations in the dataset are first arranged in ascending order.5
2. **Determine Trimming Count:** For a sample of n observations and a specified trimming percentage α (expressed as a decimal, e.g., 0.2 for 20%), the number of observations to be removed from each end of the ordered data is calculated as g = floor (α * n).

For instance, a 3% trimmed mean would involve removing the lowest 3% and the highest 3% of values.

3. **Remove Extremes:** The calculated number of observations, g, is then discarded from both the lowest and highest ends of the dataset ordered.
4. **Calculate Mean:** Finally, the arithmetic mean of the remaining n - 2g observations is computed.

The trimming percentage (α) is an important part of the trimmed means method. It determines how much of the lowest outcome data is removed before analyzing the treatment effect. While a common rule of thumb is to trim 20%, this should ideally be based on the clinical question, the data distribution, and the type of intercurrent events expected in the trial.

A more advanced approach is adaptive trimming, where the trimming percentage is based on the actual rate of missing data in the study for example, the highest proportion of missing data in any treatment group. Unlike a fixed percentage, adaptive trimming adjusts to the real trial conditions, making the estimand more accurate and robust, especially if dropout rates differ between treatment arms.

Because the trimming percentage directly affects the analysis, it must be carefully chosen and justified in the statistical analysis plan. The choice should align with the estimand definition, ensuring that the trimmed means approach properly reflects the treatment effect while accounting for intercurrent events.

**TABLE 2: DETAILED CALCULATION EXAMPLE OF A 20% TRIMMED MEAN**

| Step | Description | Example Data |
|---|---|---|
| 1. Original Sample | Initial dataset of observations. | 39, 92, 75, 61, 45, 87, 59, 51, 87, 12, 8, 93, 74, 16, 32, 39, 87, 12, 47, 50 (n = 20) |
| 2. Sorted Observations | Data arranged in ascending order. | 8, 12, 12, 16, 32, 39, 39, 45, 47, 50, 51, 59, 61, 74, 75, 87, 87, 87, 92, 93 |
| 3. Determine Trimming Count | For 20% trimming (α = 0.2) and n = 20, g = floor (0.2 * 20) = 4. | Remove 4 observations from each end. |
| 4. Trim the Observations | Remove g lowest and g highest values. | (8, 12, 12, 16) 32, 39, 39, 45, 47, 50, 51, 59, 61, 74, 75, 87 (87, 87, 92, 93) |
| 5. Calculate Mean of Remaining Observations | Compute the arithmetic mean of the bolded values. | Mean (32, 39, 39, 45, 47, 50, 51, 59, 61, 74, 75, 87) = 54.92 |
| Final Trimmed Mean | The resulting 20% trimmed mean. | **54.92** |

### B. ONE-SIDED TRIMMED MEANS (PERMUTT AND LI APPROACH)

The Permutt and Li approach is a specialized application of trimmed means, particularly suited for continuous outcomes where missing values are explicitly assumed to represent poor health outcomes.16 This method is designed to address missing data that are Missing Not At Random (MNAR), where the reason for missingness (e.g., patient dropout due to lack of efficacy) provides information about the patient's outcome.

**1. Define New Outcome (U):** For each subject i, a new outcome variable Ui is constructed. If the original clinical outcome Yi is observed (i.e., Ri = 1), then Ui = Yi. If Yi is missing (i.e., Ri = 0), Ui is assigned a value that is slightly worse than the poorest observed outcome in the trial (e.g., min(Y) - ε for a small positive ε, assuming lower values

indicate poorer outcomes). This crucial step effectively ranks all missing outcomes at the extreme tail of the distribution associated with poor outcomes.

2**. Trim Distribution:** A proportion α of the distribution of U from each treatment arm is trimmed specifically from the end associated with poor outcomes (i.e., one-sided trimming). The specific values assigned to the missing observations (min(Y) - ε) are not directly used in the final mean calculation; their purpose is solely to ensure that these observations fall below the trimming quantile. The percentage trimmed, X%, from the lower tail can be pre-specified, but it must be at least the maximum percentage of dropout observed between the two arms to ensure all "bad outcomes" are captured.

**3. Calculate Trimmed Means:** After the one-sided trimming, the arithmetic mean of the remaining 100 × (1 - α)% observations is calculated for each treatment arm (denoted as μˆT1 and μˆT0).

**4. Estimate Treatment Effect:** The final estimate of the treatment effect (μˆTΔ) is derived by taking the difference between these trimmed means: μˆTΔ = μˆT1 - μˆT0.

Inference for the Permutt and Li trimmed mean can be conducted using a permutation test. This involves conditioning on the observed data and randomly permuting treatment assignments to generate a permutation distribution of treatment differences under the null hypothesis. Confidence intervals can then be constructed by adding the 97.5th and 2.5th percentiles of this permutation distribution to the observed μˆTΔ.

#### C. STATISTICAL ASSUMPTIONS AND FORMULAS

The effectiveness of the trimmed means approach, particularly in identifying the average population treatment effect, relies on specific statistical assumptions:

**1. Missing Values as Poor Outcomes:** The method is fundamentally designed for scenarios where missing values are justifiably assumed to represent poor health outcomes.

**2. Ability to Rank Outcomes:** The approach requires that all outcomes, including those that are "missing" but assigned a "worst" value, can be meaningfully ranked.

**3. Location Family Assumption:** It is assumed that the distribution of potential outcomes for the experimental treatment (Y1) belongs to the same location family as the distribution of potential outcomes for the reference treatment (Y0). This implies that f0(y) = f1(y + Δ) for some constant Δ. This assumption is crucial because it ensures that the average difference of the entire population of counterfactuals is equivalent to the difference in the sub-population of counterfactuals that are not trimmed. This assumption is testable among the observed values and is frequently made in many statistical methods.

**4. Strong MNAR Assumption:** A conservative assumption is that all missing values fall below the point at which the distributions are trimmed. Explicitly, Ya|Ra = 0 < F−1a(α), where F−1a(α) is the α-th quantile of the distribution for arm a. This guarantees that the composite outcome Ua (which includes assigned values for missing data) is trimmed at the same value as Ya for all percentiles above the maximum rate of missing data between the two arms, and that the untrimmed distribution of Ua is identical to that of Ya. While rarely perfectly true, this assumption may hold sufficiently for dropouts primarily driven by a lack of efficacy. Numerical studies suggest that the estimator can perform well even under MNAR scenarios that are not strictly "strong MNAR," indicating a degree of robustness to slight deviations.

When both the location family and strong MNAR assumptions are plausible, the trimmed means approach can provide an estimate of the causal estimand of the treatment effect in the population. If these assumptions are not fully justifiable, the trimmed means approach can still be valuable for estimating the original composite estimand in the sub-population for which it was developed.

#### D. COMBINING TRIMMED MEANS WITH MULTIPLE IMPUTATION

In situations where the reasons for study discontinuation are known and can be categorized, the trimmed means approach can be combined with Multiple Imputation (MI) to enhance precision.

This combined methodology involves:

**1. Categorizing Missing Data:** Missing data are partitioned into observed data (Yr1), Missing At Random (MAR) or Missing Completely At Random (MCAR) data (Yr2), and Missing Not At Random (MNAR) data (Yr3).

**2. Multiple Imputation for MAR/MCAR Data:** Multiple imputation is performed specifically for the Yr2 component, assuming a valid imputation model based on the MAR assumption. This process generates m imputed datasets for Yr2.

**3. Trimming for MNAR Data:** The Yr3 (MNAR) observations are then handled by the trimmed means approach, meaning they are effectively trimmed out of the analysis after being assigned a "worst outcome" value.

**4. Calculating Trimmed Means on Imputed Datasets:** For each of the m partially imputed datasets, the trimmed means statistic (μˆ(l)TΔ) is calculated.

**5. Summarizing Results:** Rubin's rules are subsequently applied to combine the results from the m partially imputed datasets, yielding a combined estimate ($\mu T\Delta$) and its associated variance. This combined approach is considered valid only if all unobserved values of Yr3 (the MNAR component) are expected to fall below the quantile at which the distributions are trimmed.

## REGULATORY LANDSCAPE AND FDA APPROVAL

### A. ICH E9(R1) AND REGULATORY ACCEPTANCE OF ESTIMANDS

The ICH E9(R1) addendum provides a clear framework for defining estimands, which specify exactly what treatment effect a clinical trial aims to measure. This helps clinicians, statisticians, sponsors, and regulators communicate clearly about the goals of the trial and how to handle events that occur during the study.

Regulators like the EMA and FDA support this framework because it encourages transparency and precision. Sponsors are expected to clearly describe the clinical question and explain how intercurrent events will be managed, ensuring that the statistical methods match the defined estimand.

### B. EXAMPLES OF CLINICAL TRIALS USING TRIMMED MEANS AS PRIMARY EFFICACY ENDPOINT

There is limited public evidence of drug approvals where trimmed means were used as the main efficacy endpoint. Some FDA guidance mentions the method, and there are discussions about using it in trials (e.g., ophthalmology studies), but clear examples of approval based solely on trimmed means are not available.
Researchers like Permutt and Li have studied the method extensively, especially for trials where patient dropout is considered a poor outcome. Trimmed means are often used in sensitivity analyses to check the robustness of the main results, rather than as the primary endpoint. This aligns with the ICH E9(R1) guidance, which emphasizes sensitivity analyses to test assumptions about missing data and other uncertainties.

## SAS CODES FOR CALCULATING TRIMMED MEANS

### CALCULATING TRIMMED MEANS USING PROC UNIVARIATE

The PROC UNIVARIATE procedure in SAS can directly compute trimmed means by specifying the trimmed option.

```
/* Set ODS to select and output the trimmed means table */
ods select trimmedmeans;
ods output trimmedmeans=my_trimmed_means_data;

/* Invoke PROC UNIVARIATE to calculate the 20% trimmed mean */
proc univariate trimmed = 0.2 data=sashelp.shoes;
var sales; /* Specify the variable for which to calculate the trimmed mean
*/
run;
/* Optionally, view the created dataset */
proc print data=my_trimmed_means_data;
run;
```

## CONCLUSION

Trimmed means are a strong and reliable statistical method for analyzing clinical trials, especially when patients drop out or experience other intercurrent events. By removing extreme negative outcomes, this method gives a clearer picture of how a treatment works for most patients. It works well with the ICH E9(R1) estimand framework, treating dropouts or treatment discontinuation as meaningful “bad outcomes” rather than just missing data.

The method relies on important assumptions, like the strong MNAR and location family assumptions, and the choice of trimming percentage must be carefully justified. While trimmed means are statistically robust and conceptually sound, there are few publicly documented cases of FDA drug approvals where they were used as the main endpoint. Currently, they are more often used for sensitivity analyses or secondary estimands, helping to support the robustness of trial results.

With proper planning, clear assumptions, and available software tools, trimmed means can be a practical and useful tool in modern clinical trials, particularly for handling complex data and improving the interpretation of treatment effects.

## REFERENCES


1. www.investopedia.com, accessed June 5, 2025, https://www.investopedia.com/terms/t/trimmed_mean.asp#:~:text=A%20trimmed%20mean%20(similar%20to,a%20standard%20arithmetic%20averaging%20formula.

2. Trimmed Mean: Definition, Example, Calculation, and Use, accessed June 5, 2025, https://www.investopedia.com/terms/t/trimmed_mean.asp

3. What Does Trimmed Mean Mean? - Bizmanualz, accessed June 5, 2025, https://www.bizmanualz.com/library/what-does-trimmed-mean-mean

4. Robust estimation and hypothesis testing | Advanced Quantitative Methods Class Notes, accessed June 5, 2025, https://library.fiveable.me/advanced-quantitative-methods/unit-10/robust-estimation-hypothesis-testing/study-guide/jMBgGRDHYGUIvoB4

5. Trimmed means | basic statistics, accessed June 5, 2025, https://garstats.wordpress.com/2017/11/28/trimmed-means/

6. Testing treatment effects in repeated measures designs: Trimmed means and bootstrapping | Request PDF - ResearchGate, accessed June 5, 2025, https://www.researchgate.net/publication/12217838_Testing_treatment_effects_in_repeated_measures_designs_Trimmed_means_and_bootstrapping

7. The estimands framework: a primer on the ICH E9(R1) addendum - PMC, accessed June 5, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10802140/

8. ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials Training Module 1: Summary, accessed June 5, 2025, https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF_0.pdf

9. The estimands framework: a primer on the ICH E9(R1) addendum - The BMJ, accessed June 5, 2025, https://www.bmj.com/content/bmj/384/bmj-2023-076316.fu l.pdf

10. Using Estimand Frameworks in Clinical Trials | Amarex, accessed June 5, 2025, https://www.amarexcro.com/resources/using-estimand-frameworks-in-clinical-trials

11. Current developments of the estimand concept - PMC, accessed June 5, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11602887/

12. The estimands framework: a primer on the ICH E9(R1) addendum | The BMJ, accessed June 5, 2025, https://www.bmj.com/content/384/bmj-2023-076316

13. ICH E9 statistical principles for clinical trials - Scientific guideline, accessed June 5, 2025, https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials-scientific-guideline

14. www.bmj.com, accessed June 5, 2025, https://www.bmj.com/content/384/bmj-2023076316#:~:text=Composite%20strategy,Definition,endpoint%20attribute%20of%20the%20estimand.

15. Statistical Analysis Plan, accessed June 5, 2025, https://www.niaid.nih.gov/sites/default/files/statistical-analysis-plan.pdf

16. arxiv.org, accessed June 5, 2025, https://arxiv.org/pdf/1908.01044

17. An evaluation of the trimmed mean approach in clinical trials with dropout - PubMed, accessed June 5, 2025, https://pubmed.ncbi.nlm.nih.gov/29624854/

18. Identifying treatment effects using trimmed means when data are missing not at random, accessed June 5, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9051568/

19. Sensitivity to missing not at random dropout in clinical trials: use and interpretation of the Trimmed Means Estimator | medRxiv, accessed June 5, 2025, https://www.medrxiv.org/content/10.1101/2021.03.05.21252334v1

20. (PDF) Identifying Treatment Effects using Trimmed Means when Data are Missing Not at Random ResearchGate, accessed June 5, 2025, https://www.researchgate.net/publication/334986749_Identifying_Treatment_Effects_using_Trimmed_Means_when_Data_are_Missing_Not_at_Random

21. Trimmed means analysis — Study Notes - askming, accessed June 5, 2025, https://askming.github.io/study_notes/Stats/%C2%A0Note-Trimmed%20means%20analysis.html

22. www.efspi.org, accessed June 5, 2025, https://www.efspi.org/Documents/Events/Events%202018/3rd_RegStat/14%20Kardatzke.pdf

23. Trimmed Mean Analysis Is Not Rocket Science - AWS, accessed June 5, 2025, https://phuse.s3.eu-central-1.amazonaws.com/Archive/2022/Connect/EU/Belfast/PRE_AS07.pdf

24. Multiple Endpoints in Clinical Trials Guidance for Industry | FDA, accessed June 5, 2025, https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf

25. Summary - The Prevention and Treatment of Missing Data in Clinical Trials - NCBI Bookshelf, accessed June 5, 2025, https://www.ncbi.nlm.nih.gov/books/NBK209893/

26. The Prevention and Treatment of Missing Data in Clinical Trials: An FDA Perspective on the Importance of Dealing With It - AUB, accessed June 5, 2025, https://www.aub.edu.lb/SHARP/PublishingImages/Pages/publications/The-Prevention-and-Treatment-of-Missing-Data-in-Clinical-Trials-An-FDA-Perspective-on-the-Importance-of-Dealing-With-It.pdf

27. Rising API Tariffs Are Forcing Pharma to Shift R&D Resources - Applied Clinical Trials, accessed June 5, 2025, https://www.appliedclinicaltrialsonline.com/view/rising-api-tariffs-forcing-pharma-shift-resources

28. List of Guidances for Statistics in Regulatory Affairs - Wikipedia, accessed June 5, 2025, https://en.wikipedia.org/wiki/List_of_Guidances_for_Statistics_in_Regulatory_Affairs

29. Thomas Permutt's research works | U.S. Food and Drug Administration and other places, accessed June 5, 2025, https://www.researchgate.net/scientific-contributions/Thomas-Permutt-2084882277

30. Trimmed means for symptom trials with dropouts - PubMed, accessed June 5, 2025, https://pubmed.ncbi.nlm.nih.gov/27523396/

31. Complete Guide to PROC UNIVARIATE - ListenData, accessed June 5, 2025, https://www.listendata.com/2016/07/complete-guide-to-proc-univariate.html

32. (PDF) Trimmed_t: A SAS(R) Macro for the Trimmed t Test, accessed June 5, 2025, https://www.researchgate.net/publication/280556697_Trimmed_t_A_SASR_Macro_for_the_Trimmed_t_Test

**CONTACT INFORMATION (HEADER 1)**

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Prasanth Palanisamy
Company: SENSAN Biosciences
Address: Temple Steps, No.184-187, 3rd Floor, A-Block, Little Mount, Anna Salai, Chennai - 600 015.
Email: prasanth.palanisamy@sensanbio.com
Website: https://sensanbio.com/