Meaningful Change Index: A P-Value Independent Metric for Assessing Robustness and Fragility in Continuous Outcomes

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Abstract

The assessment of statistical robustness in clinical trials with continuous outcomes has relied heavily on p-value dependent metrics that fail to address clinically meaningful differences. This study introduces the Meaningful Change Index - MeCI - a novel metric applied to continuous data that quantifies how distinguishable treatment groups are based on the crossover point of their sample distributions. It is independent of statistical significance testing. The Meaningful Change Index is defined as the minimum distance from group means to their distributional crossover point, normalized by the combined standard deviations. Unlike existing continuous fragility indices that depend on p-value thresholds, Meaningful Change Index focuses on a statistically meaningful numeric separation between populations. A worked example demonstrates temporal patterns of treatment effect evolution, revealing how group distinguishability changes over time despite robust binary outcomes when arbitrary thresholds are applied to the data. Meaningful Change Index provides clinically relevant fragility and robustness assessment for continuous data

without dependence on statistical significance conventions, offering superior insights into treatment effect sustainability and group separation.

Keywords: Meaningful Change Index, MeCI, MCF, terminology update, continuous outcomes, crossover point, statistical robustness, group distinguishability, p-value independence, distributional analysis, risk quotient, fragility assessment, clinical significance

Introduction

Current approaches to assessing statistical robustness in continuous outcomes suffer from fundamental limitations. The Continuous Fragility Index (CFI) measures how many participant switches between groups are needed to alter statistical significance, but this approach remains tied to arbitrary p-value thresholds that often have limited clinical relevance (1). The dependence on p=0.05 boundaries perpetuates the problematic focus on statistical significance rather than clinically meaningful differences.

The assessment of meaningful change in clinical research has established theoretical foundations for determining when treatment effects represent meaningful change, i.e. clinically significant improvement (2). This crossover point methodology identifies the threshold where participants become equally likely to belong to functional versus dysfunctional populations. However, this framework has not been extended to fragility assessment for continuous outcomes.

This study introduces Meaningful Change Index (MeCI, pronounced MEK-see-eye), a p-value independent metric that quantifies the robustness of group separation based on distributional crossover points. Both the CFI and the MeCI are applied to continuous data. However, unlike the CFI, the MeCI is not dependent upon changes in statistical significance, which are typically rooted to an arbitrary threshold of p = 0.05. MeCI rather addresses the fundamental question: how distinguishable are treatment groups based on their underlying

population characteristics, regardless of statistical significance testing conventions? The MeCI helps determine if study findings are meaningful, if they are fragile or robust.

Methods

Theoretical Framework

MeCI is based on the crossover point between two sample distributions, representing the threshold where a value becomes equally likely to belong to either group. For two groups with means and standard deviations ($mean_1$, s_1) and ($mean_2$, s_2), the crossover point is calculated as:

$$c = (s_1 \cdot mean_2 + s_2 \cdot mean_1) / (s_1 + s_2)$$

This formula identifies the intersection point of two normal distributions with potentially unequal variances.

Meaningful Change Index Calculation

MeCI quantifies how close the nearest group mean sits to the crossover point, standardized by the combined variability:

$$MeCI = min(|mean_1 - c|, |mean_2 - c|) / \sqrt{(s_1^2 + s_2^2)}$$

The denominator represents the standard deviation of the difference between two independent groups, providing appropriate statistical normalization. MeCI interpretation follows a straightforward framework:

- Low MeCI values indicate near equivalence between groups (high fragility)
- High MeCI values indicate robust separation between groups (low fragility)

Comparison with P-Value Dependent Approaches

Unlike existing continuous fragility methods, MeCI operates independently of significance testing. This design eliminates artifacts created by arbitrary threshold selection while

focusing on the fundamental question of group distinguishability based on distributional characteristics.

Worked Example

We applied MeCI to data from the STEP 1 trial extension, which examined weight regain after semaglutide withdrawal (3). Body weight data were extracted from published results, encompassing baseline, week 68 (end of treatment), and week 120 (after withdrawal) measurements.

Continuous Data Analysis

Baseline (Week 0):

- Semaglutide: mean = 105.6 kg, SD = 21.8 kg (n=228)
- Placebo: mean = 105.4 kg, SD = 25.8 kg (n=99)
- Crossover point: c = 105.5 kg
- MeCI = 0.003

Week 68 (Peak Treatment):

- Semaglutide: mean = 87.5 kg, SD = 21.4 kg (n=228)
- Placebo: mean = 103.2 kg, SD = 25.6 kg (n=99)
- Crossover point: c = 94.6 kg
- MeCI = 0.21

Week 120 (Post-Withdrawal):

- Semaglutide: mean = 99.0 kg, SD = 22.5 kg (n=197)
- Placebo: mean = 105.5 kg, SD = 26.2 kg (n=93)
- Crossover point: c = 102.0 kg
- MeCI = 0.09

Comparison with Binary Threshold Analysis

The study authors reported that at week 120, 95 of 197 participants (48.2%) in the semaglutide group achieved ≥5% weight loss compared to 21 of 93 (22.6%) in the placebo group. Applying the Risk Quotient (RQ) (4) to this binary outcome yields moderate robustness (RQ = 0.22), suggesting meaningful treatment benefit persists.

Results

MeCI analysis reveals a clear temporal pattern of treatment effect evolution. The near-zero baseline value (0.003) confirms group equivalence before intervention. Peak separation occurred at week 68 (0.21) when semaglutide was active. By week 120, MeCI declined to 0.09, indicating diminishing group distinguishability following treatment withdrawal.

This pattern contrasts sharply with the binary threshold analysis suggesting robust treatment effects persist at week 120. The 5% weight loss threshold creates artificial robustness by dichotomizing continuous data, masking the underlying decline in group separation detected by MeCI.

Discussion

MeCI provides several advantages over existing approaches to continuous outcome fragility assessment. First, the p-value independence eliminates dependence on arbitrary statistical thresholds, focusing instead on clinically relevant group separation. Second, MeCI preserves the full information content of continuous data rather than forcing artificial dichotomization.

The worked example demonstrates how arbitrary threshold selection can create misleading conclusions about treatment robustness. While the binary analysis suggests persistent treatment benefit, MeCI reveals declining group distinguishability over time, providing more nuanced insight into treatment effect sustainability.

MeCI complements existing fragility metrics by extending robust assessment principles to continuous outcomes. Unlike continuous fragility approaches that measure p-value

sensitivity, MeCI addresses the fundamental clinical question of whether observed differences represent meaningful population distinctions.

Limitations

MeCI assumes normal distributions for crossover point calculations. The metric focuses on group-level separation and may not capture within-group heterogeneity patterns. Future research should examine MeCI performance across different distributional assumptions and clinical contexts.

Conclusion

MeCI represents a novel approach to robustness assessment for continuous outcomes that eliminates p-value dependence while focusing on clinically relevant group separation. The metric provides more nuanced insights into treatment effect patterns than binary threshold approaches, as demonstrated through the semaglutide withdrawal study. MeCI should be considered as a complementary tool for evaluating the sustainability and meaningfulness of treatment effects in clinical research.

Declarations

Data availability: All data is provided in the manuscript and cited article.

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Conflicts of interest: None declared.

Consolidation Notice

This analysis is part of an exploratory series. Related briefs may be consolidated into a master synthesis prior to journal submission.

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