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Title: The estimand framework and its application in substance use disorder clinical trials: a case study

Running Head: Estimands in SUD trials

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ABSTRACT

Relapse rates among individuals with substance use disorder (SUD) remain high and new treatment approaches are needed, which require evaluation in randomized controlled trials (RCTs). Measurement and interpretation challenges for SUD RCT data are often ignored or presented only in statistical analysis plans. As different analytic approaches may result in different estimates and thus interpretations of the treatment effect, it is important to present this clearly throughout the trial. Inconsistencies between study analyses and objectives present further challenges for interpretation and cross-study comparisons. The recent International Council for Harmonization (ICH) addendum provides standardized language and a common framework for aligning trial objectives, design, conduct and analysis. The framework focuses on estimands, which describe the treatment effect and link the trial objective with the scientific question and the analytic approach. The use of estimands offers SUD researchers and clinicians the opportunity to explicitly address events that affect measurement and interpretation at the outset of the trial. Furthermore, the use of standard terminology can lead to clearer interpretations of SUD trials and the treatments evaluated in SUD trials. Resources for understanding and applying estimands are needed to optimize the use of this new, helpful framework. This Perspective provides this resource for SUD researchers. Specifically, it highlights the relevance of estimands for SUD trials. Furthermore, it demonstrates how estimands can be used to develop clinically relevant analyses to address challenges in SUD trials. It also shows how a standardized framework can be employed to improve the interpretation and presentation of SUD study findings.

Keywords: estimand, trial, efficacy, SUD

MANUSCRIPT

Introduction

Modest remission rates for substance use disorders (SUDs) (1) and high relapse rates (2, 3) underscore the importance of randomized controlled trials (RCTs) for new treatments and new implementation strategies. However, as many as 30% of participants frequently leave SUD trials following randomization (4, 5), often resulting in missing data. Data may be missing for different reasons; for example, participants may be unable to attend study visits due to unstable living circumstances (6), or discontinue because of therapeutic toxicity.

Rubin developed a taxonomy for missing data, with three types discussed: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (7). Under MCAR, missingness is not related to observed or unobserved variables (e.g., a researcher loses a urine cannabinoid test (UCT)). Under MAR, missingness is related to observed variables (e.g., adolescents are less likely to take UCTs). Under MNAR, missingness is related to unobserved variables (e.g., relapsed participants are less likely to provide UCTs). The analytic approach for missing data, and the assumption underlying it (MCAR/MAR/MNAR), can result in different estimates of the treatment effect (8).

Another post-randomization challenge is sub-optimal adherence; in one trial for alcohol use disorder, less than half of participants in either arm attended all treatment sessions (6). Following the "intention-to-treat" (ITT) principle of analyzing all randomized participants per their assignment (9) regardless of post-randomization events such as treatment discontinuation is complicated when post-randomized data include information from those who are not on the treatment. Importantly, ITT analyses often provide estimates of the effect of assignment and may be challenging to interpret when non-adherence is high (10). An alternative is a "per-protocol" analysis, which can estimate the treatment effect under full adherence and may be of interest to patients (11), but these analyses require careful consideration (10, 12). An additional challenge is that studies may report the use of ITT, but this does not necessarily correspond to the analyses actually employed (13). Such inconsistencies pose major difficulties for cross-study comparisons and underscore the importance of standardized approaches and the clear linkage of objectives, design and analysis.

In 2019, the ICH put forth a final version of an addendum on estimands, defined as "a precise description of the treatment effect reflecting the clinical question posed by the trial objective." Major regulatory agencies such as the Food and Drug Administration are implementing the addendum (14). The framework considers post-randomization events that can affect outcome assessment or interpretation (15) and puts forth a way to link trial objectives, design and analysis using standard terms.

The importance of this development for trials is highlighted by its discussion in many clinical areas, including clinical nutrition (16), chronic pain (17) and oncology (18-20). In this Perspective, we demonstrate its application and value in a SUD context. Our aim is to provide SUD researchers with a resource for using these new, standard terms and approaches to enhance the connections between SUD trial design, analysis and interpretation.

Estimands in the SUD Trial Context: A Case Study

Per the ICH, an estimand has five attributes: treatment condition, population, variable, intercurrent events (ICEs) and the summary measure of the variable (15). ICEs are post-randomization events that can affect the measurement or interpretation of the treatment effect (15). Although ICEs are highly relevant for understanding treatment effects, they may have only been considered in statistical analysis plans rather than forming part of the scientific question (21). Different ICEs may arise in different trial and treatment contexts, even within SUD. For example, non-adherence was high in the MATCH trial (6). In the COMPASS trial, 12% of participants still smoking after treatment discontinued varenicline as they perceived it was not working (22). Other potential ICEs may include co-use of other recreational substances or concomitant medications that can affect treatment response.

The ICH estimand framework discusses five strategies for addressing ICEs. The five strategies are 1) "composite," in which the ICEs are incorporated into the outcome definition; 2) "treatment policy," similar to a "classic ITT" in that data are analyzed regardless of ICEs; 3) "hypothetical," in which the treatment effect is estimated in a hypothetical scenario of ICEs not occurring; 4) "while on treatment," in which the treatment effect prior to the ICE is estimated; and 5) "principal stratum," in which the treatment effect is estimated in a subgroup of the population defined by potential ICEs (15). Different strategies can be used for different ICEs, even within one estimand, and a trial may include multiple estimands.

In a recent trial, the Achieving Cannabis Cessation – Evaluating N-acetylcysteine Treatment (ACCENT) trial, low adherence was cited as a possible reason for a finding of lack of efficacy (23). ACCENT compared N-acetylcysteine (NAC) plus contingency management (CM) to placebo plus CM for treating cannabis use disorder (CUD). The primary outcome was abstinence, as measured by weekly UCTs (23). Other outcomes included participant-reported measures such as craving (24), measured with the validated short form of the Marijuana Craving Scale (MCQ-SF) (25, 26); the score range for this instrument is 12 – 84 (higher=more craving) (27). The primary paper, written prior to the estimand framework, highlighted both low adherence and high levels of missing data arising from missed visits as well as discontinuation. Discontinuation and non-adherence are both ICEs, whereas unavailable data as a result of missed visits is not necessarily an ICE. Depending on the scientific question, different strategies may be helpful for addressing these challenges.

To apply the estimand strategies to ACCENT, we accessed deidentified ACCENT data from the National Institute on Drug Abuse (NIDA) Data Share (https://datashare.nida.nih.gov/). We received institutional confirmation that IRB approval was not required. This is a secondary analysis for the purpose of illustration and not a formal reanalysis of the data.

Using Estimand Strategies to Answer Scientific Questions in ACCENT

In this case study, we consider two outcomes: 1) abstinence and 2) cravings. We also consider two ICEs: discontinuation and non-adherence. Of the 302 randomized participants (NAC: 153, Placebo: 149), 86 left the study prior to completion (23). In the deidentified file, a total of 92 participants were listed as ending medication early; the most common reason was study discontinuation. No participants reported discontinuation due to toxicity or perceived lack of efficacy. For our analysis, the ICE of discontinuation encompasses discontinuation for any reason. However, in other trial contexts it may be useful to treat discontinuation for toxicity or lack of efficacy as separate ICEs; such a decision would have implications for protocol design and study documentation.

In ACCENT, adherence was pre-specified as taking ≥80% of study medication per study week based on both pill counts and self-report, confirmed by riboflavin. Only 57/302 (19%) participants adhered; a more relaxed post-hoc definition without riboflavin confirmation yielded 165/302 (55%) adherent participants (23). We considered participants who took ≥80% per week over ≥80% of the weeks using self-report and pill-count to be adherent; this approach, used previously in SUD trials (22, 28-30), yielded 163 (54%) adherent participants in the deidentified file.

To begin, we reframed ACCENT's original scientific question of interest and its associated analyses using the estimand framework. As noted above, the primary scientific question was about abstinence. The odds of cannabis abstinence over time were compared between the two groups, with missing UCTs assumed to be positive/non-abstinent and the outcome assessed regardless of non-adherence (23). Table 1 shows this analysis and question using the estimand framework ("Estimand 1"). The treatment conditions are NAC+CM and placebo+CM, and the population is defined by ACCENT's inclusion and exclusion criteria: specifically, adults aged 18-50 with CUD seeking treatment. The variable for this estimand is cannabis abstinence, as measured by UCTs. There are two ICEs: discontinuation and non-adherence. In the primary paper, participants who discontinued as well as those who missed visits while on study, were assumed to be non-abstinent. The assumption that discontinuation or missingness means relapse or non-abstinence is a common one in SUD research and has been used in numerous trials (31-

33). Additionally, although this approach can produce biased results (34, 35), it is one of the criteria in the Russell Standard (36), which is frequently used in smoking cessation trials.

The approach of incorporating an ICE (here, discontinuation) into the outcome definition is consistent with a "composite strategy," as shown in Table 1. One important issue raised in the estimand is the differentiation of ICEs and missing data. As Table 1 shows, data that are unavailable due to participant discontinuation are part of the ICE and can be distinguished from data missing due to, for example, missed visits from participants remaining on study. For missing data, there was also an assumption of non-abstinence, which is consistent with MNAR missingness in Rubin's taxonomy.

The second ICE, non-adherence, is not incorporated into the outcome definition and the data are assessed regardless of adherence to treatment, consistent with a "treatment policy" strategy for this ICE. As noted previously, the treatment policy approach is similar to "classic ITT" and can estimate the effect of treatment assignment. The estimator used is a repeated measures logistic regression model with generalized estimating equations (GEE), and the summary measure is an odds ratio (OR). Following the estimand framework enables us to clearly link the analysis and objective and to differentiate between ICEs and missing data, providing greater clarity.

There was no evidence of statistically significant treatment difference between the treatment conditions for the estimand above: the OR for cannabis abstinence over time was 1.00 (95% CI: 0.63 to 1.59, p=0.984) (23). This can be interpreted as assignment to NAC+CM not increasing the odds of cannabis abstinence, as measured by urine tests, compared to placebo+CM in adults aged 18-50 with CUD seeking treatment. However, the low adherence could have underestimated a "true" treatment effect. To assess the maximum possible benefit of the treatment, we specified a "hypothetical" strategy ("Estimand 2") for both adherence and discontinuation to evaluate the treatment effect for abstinence under a counterfactual scenario of full adherence and retention.

However, in ACCENT data and in practice, participants may provide UCTs regardless of adherence. To envision an optimal scenario of adherence, we can employ UCT results from the visits where they were adherent and use this to impute what would have happened if they were always adherent. Effectively, data from visits the participant attended are "missing" if a participant is non-adherent and can be imputed such that values reflect, theoretically, values as if the participant had remained adherent. Statistically principled ways to do this include likelihood-based estimation and multiple imputation (MI) (37). For our analysis, we used MI to impute these values, which relies on the MAR assumption, and then used a logistic regression model with GEE for our estimator. Although the estimators for Estimands 1 and 2 are the same, the assumptions and strategies for addressing ICEs differ. For Estimand 2, we get an OR of 1.01 for cannabis abstinence over time (95% CI 0.61 to 1.67, p=0.97), indicating no evidence for a difference.

One explanation for the similarity of the estimates for Estimands 1 and 2 may be that NAC had little to no effect on cannabis cessation, even under an optimal scenario. Another possible explanation is the imputation model used for Estimand 2. The MI model included treatment condition and UCT results. As a further assessment, we added baseline covariates, including health-related quality of life, anxiety and depression scores and sociodemographic characteristics such as ethnicity in the imputation model, and re-estimated the estimand. This yielded an OR of 1.08 (95% CI 0.66 to 1.76, p=0.77), which did not change our interpretation. These findings highlight the importance of pre-trial planning regarding anticipated ICEs and consideration of covariates and data collection for estimand strategies such as the "hypothetical" that involve modeling.

Finally, we considered the effect on participant outcomes during treatment. Incorporating different estimands in the same trial allows for the assessment of treatment effects that may be of interest to different stakeholders (21). The "while on treatment" strategy is one strategy for answering this question. For Estimand 3 (Table 2), discontinuation is addressed through the "while on treatment" (only participant outcomes at treatment visits are of analytic interest) and adherence is addressed through the "treatment policy" strategy (assessment takes place regardless of adherence). In ACCENT, MCQ data

were collected at post-treatment follow-up, but these data are not relevant to this estimand. However, otherwise unavailable MCQ scores are considered missing data, which were addressed through MI. The estimator was a linear regression model and there was a mean difference of 1.90 on the MCQ (95% CI -2.11 to 5.90, p=0.35). This can be interpreted as no statistically significant difference in cannabis craving between the treatment conditions. Specifically, assignment to NAC+CM did not reduce marijuana cravings as measured by the MCQ at the last on-treatment visit, compared to placebo+CM in adults aged 18-50 with CUD seeking treatment.

Conclusions

It is essential to be able to compare the results of different treatments. The use of common terminology is an important aspect of this, particularly regarding critical analytic issues that can affect estimates of interest. As this case study highlights, existing data can be used to develop and understand estimands, for example through the NIDA Data Share. However, this framework will be of greatest value for planning and designing future studies, as researchers can consider possible ICEs and strategies to address them at the design stage, including the collection of any required covariates. The close linkage of objectives and analysis can also benefit studies in other fields, such as observational studies with causal inference objectives. Ultimately, better study design and the clear, careful connection of study objectives and analyses can lead to more interpretable study results and better information about treatments for SUD.

Table 1. Analyses of ACCENT Data in the Estimand Framework

Estimand Attribute or Component	**Estimand 1: Effect of Treatment on Abstinence**	**Estimand 2: Maximum Effect of Treatment on Abstinence**	**Estimand 3: Effect on Cravings During Treatment**
Scientific Question	Does NAC+CM increase the odds of cannabis abstinence over 12 weeks of treatment, as measured by urine tests, compared to placebo+CM?	Does NAC+CM increase the odds of cannabis abstinence over 12 weeks of treatment, as measured by urine tests, compared to placebo+CM, in the hypothetical situation that everyone adhered to treatment?	Does NAC+CM reduce marijuana cravings, as measured by the Marijuana Craving Questionnaire, compared to placebo+CM, while participants are on treatment (up to 12 weeks)?
Treatment Conditions	Intervention: NAC+CM Control: Placebo+CM		
Population	Adults aged 18-50 with cannabis use disorder (CUD) seeking treatment		
Variable	Cannabis abstinence as measured by urine cannabinoid test (UCT)	Cannabis abstinence as measured by urine cannabinoid test (UCT)	Cannabis craving as measured by scores on the Marijuana Craving Questionnaire (MCQ)
ICE: Discontinuation	**Composite:** Participants who discontinue treatment assumed to be non-abstinent (positive UCT)	**Hypothetical:** Participants who discontinue are assumed to have the same probability of UCT results as when observed and adhered	**While on treatment:** MCQ scores for participants are taken at their last on-treatment visit
ICE: Adherence	**Treatment policy:** UCTs assessed regardless of participant adherence to treatment	**Hypothetical:** UCTs assessed only for visits where participants adhere to treatment; when participants did not adhere, UCT results are assumed to have the same probability of cessation as when patients adhered to treatment	**Treatment policy:** MCQ scores are assessed regardless of participant adherence to treatment
Estimator	Repeated measures logistic regression model with generalized estimating equations Measurement: The outcome is measured repeatedly during the treatment period.	Repeated measures logistic regression model with generalized estimating equations Measurement: The outcome is measured repeatedly during the treatment period. Adherence is also measured repeatedly but summarized into a binary variable (≥80% study medication over ≥80% weeks), consistent with	Linear regression model

Estimand Attribute or Component	Estimand 1: Effect of Treatment on Abstinence	Estimand 2: Maximum Effect of Treatment on Abstinence	Estimand 3: Effect on Cravings During Treatment
		approaches in the literature	
Summary measure	Odds ratio (OR)	Odds ratio (OR)	Least squares (LS) mean difference
Missing Data	Imputed as non-abstinent	Data from non-adherent or discontinued participants were omitted and MI using the discriminant function method with m=100 imputations was used to impute their observations	MI using predictive mean modeling and m=100 imputations was used for participants who did not provide MCQ scores post-baseline
Assumptions about missing data	MNAR	MAR	MAR
Result	OR=1.00 (95% CI 0.63 to 1.59, p=0.98)	OR=1.01 (95% CI 0.61 to 1.67, p=0.97)	LS Mean Difference = 1.90 (95% CI -2.11 to 5.90, p=0.35)
Interpretation	Assignment to NAC+CM did not increase the odds of cannabis abstinence, as measured by urine tests, compared to placebo+CM in adults aged 18-50 with CUD seeking treatment	NAC+CM did not increase the odds of cannabis abstinence in adults aged 18-50 with CUD seeking treatment compared to placebo+CM had participants adhered to the treatment protocol and discontinuation was prevented	Assignment to NAC+CM did not reduce marijuana cravings as measured by the MCQ at the last on-treatment visit, compared to placebo+CM, in adults aged 18-50 with CUD seeking treatment

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