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Estimands and missing data in clinical trials of chronic pain treatments: advances in design and analysis

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1. Introduction

Despite the fact that a treatment for chronic pain may be prescribed for very long periods of time, possibly years, clinical trials in chronic pain typically only follow participants over a period of weeks. The primary outcome variable in these trials is often a diary-derived pain rating taken from a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable) or a 100 mm visual analogue scale (VAS) ranging from 0 to 100 with similar anchors. Although this rating is obtained at several points in time (if not daily), the primary outcome variable is usually taken to be the value obtained or derived at or near the end of the trial (e.g., the average of 7 days of ratings over the final week). This is because of overriding interest in the durability of the beneficial effect, if any, of the treatment, given that it might be prescribed over long periods of time [27].

Subject dropout is common in chronic pain clinical trials, occurring typically in 20% to 50% of trial participants [7] depending on medication, dosage, pain condition, follow-up duration, and other factors. When analyzing data from these trials, it is well-known that omitting subjects from the analysis who fail to complete follow-up (i.e., so-called “complete-case” analyses) will generally yield biased estimates of the treatment effect. Historically, methods for dealing with missing data resulting from dropout included the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) methods, or a hybrid of the two. The rationale for these methods was that, besides being easy to implement, it was thought that they would provide a conservative estimate of the treatment effect, though this is not necessarily the case (e.g., in conditions that worsen over time) [25]. These methods are also known to yield biased estimates of treatment effects in general. Even in the rare case

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where such imputation might be sensible (e.g., if subjects would have returned to their baseline state after dropout for the remainder of the trial), these methods tend to underestimate the variance of the estimated treatment effect and can lead to inflation of the probability of a Type I error. The vast literature on the poor statistical properties of these methods is well summarized elsewhere [18,25].

In 2010, the National Research Council (NRC) published a report on *The Prevention and Treatment of Missing Data in Clinical Trials* [25] that has led to increased attention to how missing data are handled in the analysis of clinical trial data. The report's emphasis on prevention is particularly important because any statistical method for dealing with missing data ultimately relies on untestable assumptions, and the influence of incorrect assumptions on the results is minimized when the occurrence of missing data is minimized. Despite this, the occurrence of missing data will likely remain ubiquitous in chronic pain clinical trials. We believe that a recently proposed method commonly referred to as control-based (or reference-based) imputation can be highly useful in dealing with the problem of missing data in chronic pain clinical trials [1–3,20,26]. In this paper, we illustrate this approach and contrast it with existing approaches using data from four clinical trials of pregabalin, two in painful diabetic peripheral neuropathy (DPN) and two in postherpetic neuralgia (PHN).

2. Methods

2.1. Source of Clinical Trial Data

Through the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership, the FDA granted the authors access to data from 12 randomized, double-blind, placebo-controlled clinical trials of pregabalin for the treatment of various chronic pain conditions that were submitted to the FDA. Dosages of pregabalin used in these trials varied from 75 mg/day to 600 mg/day, and durations of double-blind follow-up varied from 5 weeks to 13 weeks over the 12 trials (Table 1).

Four out of the 12 clinical trials were selected to illustrate the results of applying different missing data approaches on inference concerning the effect of pregabalin. These specific trials were selected because two involved subjects with DPN and two involved subjects with PHN, and all used dosages up to 600 mg/day and had their results published [5,9,30,36]. The primary outcome variable in all of these studies was the rating of average pain on a 0–10 NRS, averaged over the 7 daily ratings provided *before* the final double-blind visit. For purposes of our re-analyses of these four trials, the ratings of average pain on the NRS were also averaged over the seven days *before* each earlier (intermediate) visit; if fewer than seven diary entries were available *before* a given visit, the average over the available entries was used unless there were fewer than 4 diary entries in the week *before* that visit, in which case the outcome for that visit was considered to be missing.

2.2. Classification of Reasons for Dropout

For each of the 12 clinical trials of pregabalin, reasons for dropout were captured using the following categories: adverse event (AE), lack of compliance, lack of efficacy, loss to

follow-up, withdrawal of consent, and other. Under the category of “other”, additional detailed text was provided by site personnel to explain the circumstances surrounding the early withdrawal. Each text description ($n = 228$) was reviewed and classified by one of the authors (XC) and verified by another author (JSG); any disagreements were resolved by consensus after consultation with a third author (RHD). In cases that were difficult to classify, relevant information on the case, if any, was obtained from the Clinical Study Report (CSR) and used in the classification process. Reasons for dropout originally classified as “other” were reclassified as follows based on review of the text: (1) Protocol violation: if this was clearly stated in the text (e.g., the subject took a medication that was prohibited by the protocol); (2) Unrelated reason: if the subject dropped out for a reason that was clearly not related to his/her experience in the trial (e.g., the subject had to take care of a sick relative or was called to jury duty); (3) Unclear: if there is no indication in the text as to why the subject dropped out; (4) Loss to follow-up: if this was clearly stated in the text; (5) Withdrawal of consent: if the text indicated that the subject withdrew consent and there was no evidence that it was for a reason unrelated to his/her experience in the trial; (6) Adverse event: if there was an AE listed in the text as a reason for dropout; (7) Ineligible: if it was discovered after randomization that the subject was not eligible for the study; and (8) Patient withdrawn in error: if this was clearly stated in the text.

2.3. Existing Methods for Handling Missing Data

2.3.1. Methods based on the Missing at Random Assumption—In contrast to ad hoc methods such as LOCF and BOCF, more principled methods for handling missing data have existed for several years, including the mixed-model repeated measures (MMRM) approach [16], multiple imputation [4,32,33], and weighted generalized estimating equations [21], with MMRM perhaps being the most commonly used in chronic pain clinical trials. It is important to consider, however, that each of these methods depends on the missing at random (MAR) assumption [31]. One way to think about this assumption is to consider two subjects with similar baseline characteristics who are randomized to the same treatment group and have the same pattern of pain outcomes up until a certain point in the trial when the first subject drops out; the second subject goes on to complete the trial. The MAR assumption implies that the first subject, had he/she remained in the trial, would have had similar responses to the subject who completed the trial [20]. This assumption is untestable.

The MAR assumption might be plausible, for example, for subjects who drop out due to a perception of poor efficacy, since their pattern of observed pain ratings (and other information) *before* dropout may predict well what their pain ratings would have been had they remained in the trial, regardless of what treatment they were assigned. On the other hand, subjects who drop out due to an AE, particularly if they were assigned to receive an effective treatment, may have had a good analgesic response up until the time of the AE. The MAR assumption may or may not be reasonable depending on the quantity that is of interest to estimate, i.e., the *estimand*. If the estimand is the effect of treatment if all subjects remained on treatment, then the MAR assumption may be plausible, although a natural criticism of this estimand is that it may result in favorable outcomes being given to those who dropped out because they could not tolerate the treatment. The MAR assumption would not be tenable, however, if the estimand were the effect of treatment if subjects who dropped

out received no further in- or out-of-protocol treatment. In this case, a subject who could not tolerate the treatment, even if effective, would not benefit from it after dropout. Overly optimistic post-dropout outcomes would be implicitly imputed for this subject under the MAR assumption [20].

2.3.2. Methods that Classify Dropouts as Having Poor Outcomes—Other methods have been proposed that treat subjects who drop out as having had a poor outcome, regardless of the reasons for dropping out. One proposal is to use what are termed “responder analyses”, with the outcome variable being defined as having achieved a certain percentage or absolute reduction in pain rating from baseline (e.g., 30% or 50%); those who fail to complete the trial are assigned “non-responder” status [22,24]. *Alternatively, in view of patient preferences, a “responder” could be defined as one who has “no worse than mild pain” [23], perhaps with no intolerable adverse events.* A weakness of these methods is that dichotomizing the changes in pain ratings into “responder” and “non-responder” categories sacrifices information, typically resulting in larger sample size requirements. Also, the choice of the cut-off for defining a good response is not always clear and may depend on the pain condition under study.

Another proposed method by Permutt and Li [28] is based on trimmed means. In this method, the outcomes in each treatment group are ordered from worst to best, and the group difference in mean outcome is computed after omitting the same percentage of the worst outcomes (e.g., the worst 30%) from each treatment group, with the percentage chosen *a priori* to exceed the expected percentage of dropouts in either group. Permutation methods are used to obtain p-values and confidence intervals for inference concerning the treatment effect. A useful generalization of this method using quantile regression for estimation and the bootstrap for inference was provided by Mehrotra et al. [20] The estimand in this case (difference in the means between the treatment groups in the subjects with the best, say, 70% of outcomes in each group), however, is not as easily interpreted as a simple group difference in means.

Both “responder analyses” and the trimmed means approach described above are predicated on the assumption that those who drop out of a clinical trial have a poor outcome. This may or may not be reasonable depending on the reasons for dropping out. Someone who drops out because he/she is unable to tolerate the treatment might be considered to have a poor outcome. It might not be reasonable, however, to assign a poor outcome to someone who drops out for reasons unrelated to treatment. Participation in a clinical trial can be burdensome for subjects, and changes in life circumstances may make trial participation more difficult if not impossible. The fact that someone is unwilling to continue to receive a treatment in a clinical trial does not directly imply that the person would not be willing to continue to receive the treatment in clinical practice. Permutt and Li [28] state that “A patient who drops out for a reason known to be unrelated to treatment has not necessarily had a bad outcome and might be best handled as missing at random (MAR), but such dropouts are necessarily equally likely across treatment groups, so that handling them, like other dropouts, as bad outcomes produces no bias.” This statement is not correct. If subjects are equally likely to drop out of both treatment groups and the active treatment is superior to placebo, then under MAR the estimated treatment effect will likely be positive among

subjects who drop out, and assigning all of them equally poor outcomes will indeed bias the estimated treatment effect toward the null. A strong argument can be made in this case for not penalizing the effective treatment for the occurrence of dropouts that are known to be unrelated to the treatment.

2.4. Estimands—The 2010 NRC report highlighted the importance of careful specification of the trial objectives and estimands of interest in clinical trials [25]. This issue has since received a great deal of attention [10,11,17,18,27,29] and motivated an addendum to the International Conference on Harmonization (ICH) E9 guidance on Statistical Principles for Clinical Trials, currently in draft form [6]. An estimand is the population quantity to be estimated in terms of the target population, outcome variable, handling of post-randomization (intercurrent) events, and population-level summary for the outcome variable [6,10,25]. Intercurrent events that arise in many chronic pain trials include dropout from the trial, discontinuation of trial medication, reduction in the dosage of trial medication, use of rescue medication, and use of an out-of-protocol treatment. Some examples of estimands from the NRC report that are particularly relevant to chronic pain trials include the following [17,25]:

1. *Difference in mean outcome at the planned endpoint for all randomized participants (strict intention-to-treat [ITT] estimand).* This estimand compares the policies of assigning the different treatments with respect to mean outcome at, say, the final time point, regardless of any intercurrent events that might occur. This represents what some would consider to be very strict adherence to the intention-to-treat principle and addresses a pragmatic effectiveness question concerning the treatment that may not be relevant in many settings. This estimand, therefore, is rarely of primary interest, especially *before* regulatory approval. With this estimand, it is very important to collect data from all subjects at the final time point because dealing with missing data in this setting is challenging without knowledge of how subjects are treated after dropout.
2. *Difference in mean outcome at the planned endpoint in those who tolerate the treatment (effect in tolerators estimand).* This estimand applies to only a subset of the target population that would be exposed to the treatment. If this were the estimand of interest, an enriched enrollment randomized withdrawal (EERW) design [19] could be used to yield an estimate. The estimand does require further specification, however, regarding how to handle intercurrent events, including the missing data from those who drop out of the trial, as in the two estimands below.
3. *Difference in mean outcome for all randomized subjects at the planned endpoint that would have been obtained if all subjects tolerated and complied with treatment (de jure estimand).* This *de jure* [3] estimand addresses the issue of pure efficacy, i.e., what would be expected in the “best case” scenario, rather than effectiveness.
4. *Difference in mean outcome for all randomized subjects at the planned endpoint that is attributable to the initially randomized treatment (de facto estimand).* This *de facto* [3] estimand assesses the effectiveness of the treatment at the planned

endpoint, but differs from the first estimand above in that it is not confounded by the effects of protocol-specified rescue medication or out-of-protocol treatment. As a result, the problem of dropout is somewhat easier to address, as we will discuss below.

It is clear from the above that the study objectives and the definition of the estimand(s) of interest need to be specified before deciding on the study design, what data to collect, and how the data should be primarily analyzed [11]. Historically, clear specification of the estimand has often been lacking, resulting in the trial not optimally addressing the question of primary interest. Only after the estimand(s) of interest have been specified can one rationally determine answers to questions such as: (1) Should outcome data be collected after discontinuation of treatment, or after introduction of protocol-specified rescue medication or out-of-protocol treatment (effectiveness estimand), or should the subject be withdrawn from the trial at that point (efficacy estimand)? (2) Should a run-in period to assess tolerability of the treatment be incorporated in the trial design (EERW)? (3) How should missing data be handled in the statistical analysis? The NRC report recommends collecting data after treatment discontinuation or introduction of rescue medication or out-of-protocol treatment. This allows data to be analyzed in various ways [10,25], but one has to consider the costs and benefits of obtaining such data given the estimand(s) of interest.

The choice of the primary estimand may differ depending on the scientific question, the stage of development of the treatment, and the stakeholders (e.g., regulators, sponsors, patients, and prescribers), among other things [11]. Indeed, many estimands may be of interest in a single trial, *and a sound argument can be made that they should all be included in a clinical trial report.*

2.5. Control-based Imputation

The recent emphasis on defining the trial estimand makes it clear that methods are needed to handle missing data in chronic pain clinical trials beyond simple, ad hoc approaches and even those that assume MAR for all subjects who drop out. The MAR assumption may be useful when interest centers on the *de jure* estimand above, the difference in mean outcome for all randomized subjects at the planned endpoint that would have been obtained if all subjects tolerated and complied with treatment. An analysis using MMRM or a standard application of multiple imputation, for example, after excluding any outcomes that were obtained after introduction of protocol-specified rescue medication or out-of-protocol treatment, could yield an appropriate estimate of the treatment effect in this case. For other estimands, however, such as the *de facto* estimand above, the difference in mean outcome for all randomized subjects at the planned endpoint that is attributable to the initially randomized treatment, a different assumption concerning missing data would be needed. While the analysis would still exclude outcomes that were obtained (if any) after introduction of protocol-specified rescue medication or out-of-protocol treatment, a global MAR assumption would be less plausible, especially for subjects who drop out due to an AE, for example. If the treatment had a positive effect on a subject's outcome but the subject could not tolerate it, the MAR assumption would continue to yield favorable pain outcomes for a subject in the active treatment group, which would be overly optimistic. Using BOCF to impute outcomes for this subject, on the other hand, may also be misleading (i.e., overly

pessimistic), particularly in the setting of placebo effects or other effects of study participation such as increased attention from clinical trial staff [18]. Because the *de facto* estimand is often of interest in clinical trials of chronic pain, we will focus on this estimand in what follows below.

Control-based (or reference-based) imputation is a method proposed by Carpenter et al [3], motivated by ideas in Little and Yau [12] that allows one to make various assumptions concerning the distribution of outcomes in those who drop out, conditional on their observed outcomes, treatment group, and possibly other subject characteristics. Missing not at random (MNAR) assumptions can be made where the probability of a value being missing depends on the unobserved (missing) outcomes, not just the observed outcomes as is the case with MAR. Advantages of this method include its flexibility in accommodating a variety of assumptions and its transparency with regard to the assumptions that are being made concerning outcomes after dropout.

Control-based imputation is particularly useful for the case where the *de facto* estimand above is of primary interest. A common implementation of this method is to assume MAR for subjects who drop out in the placebo group, with the thought that such a subject would have outcomes after dropout that are like those in placebo-treated subjects who completed follow-up and had a similar outcome pattern *before* the time the subject dropped out [26]. The method then requires an assumed model for the conditional distribution of outcomes in subjects who drop out of the treatment group. For the *de facto* estimand considered here, an assumption called “jump to reference”, or J2R, might be appropriate, particularly for trials of analgesic treatments with purely symptomatic effects that disappear relatively soon after treatment withdrawal. This assumption implies that outcomes after dropout immediately switch to be like those from subjects in the placebo group. One can even take into account the subject’s deviation from the average pattern of outcomes in the treatment group before dropout and assume that the subject would similarly deviate from the average pattern of outcomes in the placebo group [26]. A variety of other assumptions concerning the conditional distribution of outcomes among dropouts from the treatment group can be made, such as “copy reference” (CR) where the outcomes after dropout gradually switch to be like those from subjects in the placebo group, and “copy increment from reference” (CIR) where the outcomes after dropout have a trajectory over time that matches that of the placebo group, but the effect of treatment up until the time of dropout is maintained until the end of the trial (e.g., as might be expected of a treatment that has a permanent effect after withdrawal). Figure 1 illustrates imputations of outcomes after dropout for a subject in the treatment group according to the MAR, J2R, CR, and CIR assumptions. A variety of other assumptions are possible that can be tailored to the estimand of interest [3,26]. Importantly, one of the features of this approach is that one can make different assumptions concerning the conditional distribution of the post-dropout outcomes depending on the stated reasons for dropping out [3,26]. Note that for purposes of the above discussion, dropout can refer to an event where the subject has an intercurrent event (e.g., use of rescue medication or out-of-protocol treatment) *before* the end of follow-up that results in the exclusion of any data collected at or after that event for purposes of statistical analysis.

Control-based imputation can be implemented in a variety of ways including multiple imputation using pattern mixture models [1,3,26] and a likelihood-based method in which explicit subject-level imputation is not required [20]. The multiple imputation approach is known to yield an overestimate of the variance of the treatment effect [15,20,34,35]. Although control-based imputation has been promoted as a highly useful approach to performing analyses to examine the sensitivity of the results of the primary analysis to assumptions concerning the missing data mechanism [1,3,14,20,26], it might be appropriate for the primary analysis of a clinical trial depending on the estimand of primary interest (e.g., the *de facto* estimand above).

Several authors have performed simulation studies to evaluate various methods for dealing with missing data in terms of their statistical properties (e.g., bias, Type I error probability, confidence interval coverage probability, and power) under various assumptions [14–17,20,27]. The purpose of this study is to illustrate the consequences of the choice of the approach to the missing data problem using actual data from the four clinical trials that we selected, which vary somewhat in their frequencies and reasons for dropout.

2.6. Statistical Methods

For each of the four trials selected for formal analysis, only the placebo group and the groups that were assigned at least 300 mg/day of pregabalin (i.e., dosages that were presumed to be efficacious) were included. The data were analyzed using an analysis of covariance model for the change in NRS score from baseline to the final week with treatment group and baseline NRS score included as independent variables. We considered two multiple imputation strategies. The first strategy assumed MAR for all dropouts, which typically yields results similar to those from the MMRM approach that is commonly used and would be more appropriate for the *de jure* estimand; separate imputation models were used for each treatment group and included observed outcomes at all visits *before* dropout for the subject [3]. The second strategy assumed J2R for subjects in the pregabalin group(s) who dropped out due to an AE and MAR for all other dropouts as well as for intermediate missing data. This strategy assumes that those in the pregabalin group(s) who drop out due to an AE will have post-dropout outcomes that are similar to those in the placebo group. For those who dropped out due to a lack of efficacy, it was assumed that their observed outcomes (and outcomes of similar subjects who completed follow-up) would reasonably predict their outcomes after dropout had they remained in the trial. Pregabalin is rapidly absorbed and eliminated; therefore, the assumption that the pain outcome will jump to reference (J2R) after subject dropout from the treatment arm due to an AE is reasonable for the *de facto* estimand. The number of imputations used to estimate the treatment effect and its corresponding 95% confidence interval was 40. For both the *de jure* and *de facto* estimands, the target population was defined by the trial eligibility criteria, the outcome variable was the change from baseline to the final week in NRS score, and the population-level summary for the outcome variable was the treatment group difference in mean change from baseline to the final week in NRS score. In all four trials, the intercurrent events of discontinuation of trial medication and use of an out-of-protocol treatment were grounds for withdrawal of the subject from participation. Data obtained from subjects who used rescue medication that was permitted in the protocol were included in the analyses.

Other methods for dealing with missing data were used, including removing subjects who dropped out from the analysis (complete cases, or CC), LOCF, BOCF, and the trimmed mean approach [28] (which actually considers dropout to be a poor outcome and not as an event yielding missing data). For the latter method, two strategies for trimming were examined: (1) trimming the worst 50% of outcomes (including all dropouts) and (2) an adaptive trimming strategy whereby all dropouts are trimmed for the group with the largest percentage of dropouts and the same percentage of subjects with the worst outcomes (including all dropouts) are trimmed from the other group. The estimated treatment effect (group difference in the means in the subjects with the best X% of outcomes in each group) and associated 95% confidence interval were estimated using 30,000 permutations.

3. Results

3.1. Frequencies of and Reasons for Dropout

The total number of subjects included in the 12 trials examined was 3,501. The chronic pain conditions, sample sizes, pregabalin dosages, and follow-up schedules in these trials are summarized in Table 1. Among the 12 trials, 4 were in DPN, 4 were in PHN, 2 were in chronic low back pain, and 1 each were in osteoarthritis and fibromyalgia.

Table 2 provides detailed reasons for early withdrawal for each protocol regardless of treatment group, including only data from the placebo group and the pregabalin groups receiving either 300 mg/day or 600 mg/day. The most common reasons for dropout were AE (12.7% overall; range 6% to 24%) and lack of efficacy (5.7% overall; range 1% to 15%). Also, the dropout percentages due to unclear reasons varied from 0% to 8% even after our detailed text review.

Table 3 shows the percentages of randomized subjects in each study who dropped out due to an AE and who dropped out for any other reason (non-AE) for the placebo, pregabalin 300 mg/day, and pregabalin 600 mg/day groups. Dropouts due to AEs were more frequent in the pregabalin groups, particularly in the 600 mg/day group, than in the placebo group, whereas dropouts for other reasons were more common in the placebo group. Figure 2 shows the trajectories of individual pain scores over time in the 4 protocols of primary interest (014 and 029 in DPN, 127 and 196 in PHN) for pregabalin-treated subjects who dropped out due to an AE and all subjects who dropped out for other reasons, with placebo- and pregabalin-treated subjects distinguished by line type. Those who dropped out due to an AE did so generally early in follow-up and were predominantly in the pregabalin groups. Their pain scores also tended to improve up until the time of dropout. For those who dropped out for other reasons, the trajectories of pain scores over time did not demonstrate a clear pattern.

3.2. Re-analyses of Selected DPN and PHN Clinical Trials of Pregabalin

Protocol 014: In this trial, 82 subjects with DPN received 600 mg/day of pregabalin and 85 received placebo. Figure 3a shows the crude (no imputation for missing data) mean pain scores for subjects in the 2 treatment arms, indicating that subjects in the 600 mg/day group had greater improvement of pain in the first 2 weeks than subjects in the placebo group, with continued separation of the groups up to Week 6. Figure 3b shows the estimated treatment

effects at Week 6 and associated 95% confidence intervals when different approaches to missing data were used. Dropout percentages were relatively small and similar in the two groups (16.5% placebo; 14.6% pregabalin), with a slightly higher percentage due to AEs in the pregabalin group (Table 3). Perhaps due to the relatively small amount of missing data, the estimated treatment effects did not vary greatly between the approaches although, as expected, the BOCF, LOCF, and J2R strategies yielded the smallest estimates. Of note, the 50% trimmed mean strategy provided the largest estimated treatment effect and widest associated confidence interval. All estimated treatment effects were statistically significant, as indicated by none of the confidence intervals overlapping the value of zero.

Protocol 029: In this trial, 82 subjects with DPN received 600 mg/day of pregabalin, 81 received 300 mg/day of pregabalin, and 97 received placebo. Figure 4a shows the crude mean pain scores for subjects in the 3 treatment arms, indicating similar treatment effects in the 300 mg/day and 600 mg/day pregabalin arms relative to placebo. Dropout percentages were small in the placebo (14.4%) and 300 mg/day (16.0%) groups with < 4% dropping out due to an AE. In contrast, 20.7% of subjects dropped out in the 600 mg/day group, with 12.2% dropping out due to an AE (Table 3). Figures 4b and 4c show that, as in Protocol 014, the trimmed mean strategies provided the largest estimated treatment effects in both active treatment arms. In the 300 mg/day arm, the treatment effects were similar in magnitude for the other approaches to missing data, with BOCF and J2R providing the smallest estimates of treatment effect. In the 600 mg/day arm, the LOCF and MAR strategies showed larger treatment effects due to the greater number of dropouts due to an AE and the fact that these subjects tended to have improved pain scores up until the time of dropout. The BOCF strategy again produced the smallest estimated treatment effect in this case. As in Protocol 014, all estimated treatment effects were statistically significant for both dosages of pregabalin.

Protocol 127: In this trial, 89 subjects with PHN received either 300 mg/day or 600 mg/day of pregabalin and 84 received placebo. The 300 mg/day dosage was given if the subject's creatinine clearance was below normal (30–60 mL/min). Figure 5a shows the crude mean pain scores for subjects in the 2 treatment arms, indicating that subjects in the pregabalin group had greater improvement of pain in the first 3 weeks than subjects in the placebo group, and that this effect was maintained through Week 8. The dropout percentage was relatively small in the placebo group (11.9%) and quite large (34.8%) in the pregabalin group, with nearly all of the dropouts in this group (28/31) due to an AE (Table 3). Given the general improvement in pain scores up until the time of dropout for subjects who dropped out due to an AE (Figure 2), it is not surprising that the LOCF strategy for dealing with missing data yielded a large estimated treatment effect (Figure 5b), although it is somewhat surprising that the MAR strategy yielded such a small estimate. The BOCF and J2R strategies, as expected, also yielded smaller estimated treatment effects. The confidence intervals were quite wide for the trimmed mean strategies, which also yielded large treatment effects. Of note, the statistical significance of the treatment effects depended on the strategy used for dealing with missing data.

Protocol 196: In this trial, 90 subjects with PHN received either 300 mg/day or 600 mg/day of pregabalin (depending on the subject's creatinine clearance, as in Protocol 127), 98 received 300 mg/day of pregabalin, and 93 received placebo. Figure 6a shows the crude mean pain scores for subjects in the 3 treatment arms, indicating that 300/600 mg/day and 300 mg/day groups had greater improvements of pain in the first 4 weeks than subjects in the placebo group, with the effect in the 300 mg/day group waning somewhat by Week 13. The dropout percentages were very high in all three treatment groups: 44.1% in the placebo group, 42.9% in the 300 mg/day group, and 37.8% in the 300/600 mg/day group, with dropout due to an AE more common with increasing dosage of pregabalin (Table 3). Figures 6b and 6c show that, as expected in this case, the BOCF and J2R strategies for missing data yielded the smallest estimated treatment effects. This was especially true for the 300/600 mg/day treatment group, in which a greater percentage of dropouts were due to an AE. The 50% trimmed mean strategy yielded the largest estimated treatment effects. The narrower confidence intervals for the LOCF and BOCF strategies in the setting of a high percentage of missing data illustrate the false precision that these approaches often yield in such cases [17,23]. As in Protocol 127, the statistical significance of the treatment effects depended on the strategy used for dealing with missing data, especially for the 300 mg/day group.

4. Discussion

The release of the NRC report on *The Prevention and Treatment of Missing Data in Clinical Trials* [25] and draft addendum to the ICH E9 guidance on Statistical Principles for Clinical Trials [6] signify a major shift in how clinical trialists think about trial design and analysis. The NRC report emphasizes measures that trialists can take at the design stage to reduce the occurrence of missing data, the importance of which cannot be overstated given the dependence of any statistical method for accommodating missing data on untestable assumptions. *For example, in an analysis of pooled data from 3 clinical trials of tapentadol and oxycodone for chronic osteoarthritis pain and low back pain, with up to 40–60% of participants discontinuing treatment, different methods for dealing with missing data yielded treatment effect estimates that differed in both magnitude and direction* [8]. Moreover, given that missing data are unavoidable, the report draws attention to the significant limitations of existing simplistic methods such as LOCF and BOCF and emphasizes the use of more principled methods to deal with the problem.

Both the NRC report and the draft addendum to ICH E9 (especially the latter) speak to the importance of precise formulation of the estimand(s) of interest based on the study objectives. In particular, much thought needs to be given to how to deal with intercurrent events in formulating the estimand; this exercise is ideally carried out as a collaborative effort between clinicians and statisticians, and many useful examples are provided in the draft ICH E9 addendum [6]. In the context of chronic pain trials, besides dropout, common intercurrent events include discontinuation of study medication, use of prohibited medications, and use of permitted rescue medication. The four pregabalin protocols on which our illustrative analyses were based mandated discontinuation of participation of subjects who discontinued study medication or used prohibited medications, limiting the estimands that could be considered in our analyses. It can be useful to examine multiple

estimands in the same trial so that information relevant to multiple stakeholders can be derived.

Statistical methods that are well-suited to yield appropriate estimates of the treatment effect arise from the specification of the estimand. Control-based imputation is a useful and flexible method to deal with the problem of missing data resulting from intercurrent events that can be applied for a wide variety of estimands. A special case of this is to assume that the missing data are MAR, as do many commonly employed methods such as MMRM and multiple imputation, and this may be perfectly suitable for the *de jure* estimand considered in our analyses. For the *de facto* estimand, we made the assumption that those in the pregabalin group(s) who dropped out due to an AE would have outcomes similar to those in the placebo group after the time of dropout (J2R). Also, it was assumed that subjects with missing data for all other reasons, had they remained in the trial, would have had outcomes that are reasonably well predicted by their observed outcomes and the outcomes of similar subjects who completed follow-up. Intermediate missing outcomes were assumed to be MAR, which is likely to be reasonable in most cases [3,26]; their occurrence tends to be relatively rare in practice.

One could certainly make the case that the missing data from those who dropped out due to a perceived lack of efficacy in the pregabalin group(s) should also have been considered J2R. This is not a clear-cut issue. For example, it could also be argued that people may have different expectations concerning pain relief when they enter a clinical trial. A certain degree of pain reduction for one subject might not be satisfactory for another subject, causing the latter subject to drop out, even though the pain reduction is better than that which would have been achieved on placebo. It might be reasonable to assume MAR in this case, or something in between MAR and J2R. This illustrates the need to recognize and carefully defend any assumptions that are made when using control-based imputation. Our examples illustrate the use of one set of assumptions, but these are not necessarily the most appropriate in any particular setting; it is important to emphasize that the approach selected will depend on the trial objective and estimand of interest. An advantage of control-based imputation is the transparency regarding the assumptions that are made concerning the conditional distribution of outcomes after dropout in those who do not complete follow-up.

There are some limitations associated with the use of control-based imputation. Clearly, it should be used with caution in cases where it is quite possible for the treatment to be inferior to placebo (e.g., with safety outcomes). Similarly, one has to carefully consider how to formulate the estimand of interest in studies in which there is no placebo control group. Also, study planning (sample size determination) will require information on the frequency of intercurrent events that may affect the primary estimand of interest.

The dependence of statistical methods for handling missing data on untestable assumptions concerning the missing data mechanism underscores the importance of performing sensitivity analyses that examine how the results concerning the treatment effect vary with departures from the original assumptions. This was a major point of emphasis in the NRC report [25]. The so-called “ δ -adjustment” method allows the specification of a value δ representing the difference in, say, mean outcome between those who complete the trial and

those who do not, with possibly different values of δ (δ_1 and δ_0) used for the different treatment groups (note that in this formulation, $\delta = 0$ would correspond to MAR). One can then present the results for different values of δ_1 and δ_0 [13,25] and indicate which values would lead to a failure to reject the null hypothesis of no treatment effect in a so-called “tipping point” analysis [37]. If the qualitative nature of the results is maintained for all clinically plausible values of δ_1 and δ_0 , then the treatment effect would be considered to be robust [13]. The control-based imputation approach lends itself to sensitivity analyses that can be easily applied in various ways [3,14,20,26,35].

Among the 12 trials in which we examined the stated reasons for dropout, approximately one-third of the dropouts were not recorded to be due to either an AE or a lack of efficacy. The trimmed means approach, which assigns poor outcomes to all subjects who drop out, may be reasonable if one believes that failure to complete follow-up for any reason is itself a poor outcome, but it is not clear that this is the case in the setting considered here. This method tended to yield larger values of the estimated treatment effects and wider confidence intervals in our analyses; the estimand in this case is the difference in group means for the subjects with the best 50% of outcomes in each group. The approach using adaptive trimming often yielded smaller estimated treatment effects, perhaps reflecting that the effect of pregabalin relative to placebo was not a constant shift in the distribution of outcomes.

Reasons for dropout and other intercurrent events in chronic pain clinical trials vary substantially from those that are unrelated to the study protocol to those that are directly caused by the treatment assigned to the subject. Different estimands will require different strategies for dealing with these intercurrent events in the statistical analysis. A valuable feature of control-based imputation is that one can accommodate different assumptions concerning the conditional distribution of post-dropout outcomes depending on the stated reason for dropout. If such information is to be used, however, it is imperative to ensure that specific reasons for dropout are thoroughly and accurately ascertained. The collection of this information can be quite variable from trial to trial, and complicating factors include (1) not all subjects are willing to provide a reason for dropout and (2) the reasons for dropout are often multifactorial. In the 12 pregabalin trials that we examined, there were 228 stated reasons for dropout that were classified as “other”, and even after detailed review of the textual information that was provided, a substantial percentage of reasons for dropout were classified as “lost to follow-up”, “withdrawal of consent”, and “unclear”. More work is needed to develop improved standards for collection of these data, and more thought is needed regarding how to use the information in a way that yields appropriate estimators for various estimands of interest.

There has been a realignment of the framework for trial planning that starts with formulation of the trial objectives and precise definition of the estimand(s) of interest, informing the trial design and the statistical methods to deal with intercurrent events and the resulting missing data [6,10]. Control-based imputation is a flexible method for this purpose that can be applied for a wide variety of estimands and can be used to perform sensitivity analyses to examine the robustness of the trial results to assumptions concerning the missing data mechanism. Researchers conducting clinical trials of treatments for chronic pain conditions should consider using control-based imputation to derive appropriate estimates of *de facto*

estimands for the primary analysis of treatment effects. This can be supplemented with other methods such as the comparison of trimmed means[28] and “responder analyses” as well as estimates of other estimands of interest to stakeholders [20].

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Figure 1.

Illustration of typical imputed values for a subject in the treatment group that drops out of the trial after Week 1 for four different assumptions concerning the missingness mechanism. The black squares (■) are the observed means in the placebo group and the open squares (□) are the observed means in the treatment group. The asterisks represent either observed (Weeks 0 and 1) or imputed (Weeks 3, 5, and 8) values for the subject who dropped out of the trial.

Figure 2.

Subject dropout patterns for each of the four pregabalin protocols. Left panels: dropout due to an adverse event (AE) in the pregabalin arms; right panels: all other dropout.

Figure 3.

Crude mean pain scores at each visit among participants in Protocol 014 (Panel a), and estimated treatment effects (active – placebo) and corresponding 95% confidence intervals for pregabalin 600 mg/day (Panel b) using different methods for handling missing data. LOCF = Last observation carried forward; BOCF = Baseline observation carried forward; MAR = Missing at random; J2R = Jump to reference (control-based imputation).

Protocol 029

Figure 4.

Crude mean pain scores at each visit among participants in Protocol 029 (Panel a), and estimated treatment effects (active – placebo) and corresponding 95% confidence intervals for pregabalin 300 mg/day (Panel b) and pregabalin 600 mg/day (Panel c) using different methods for handling missing data. LOCF = Last observation carried forward; BOCF = Baseline observation carried forward; MAR = Missing at random; J2R = Jump to reference (control-based imputation).

Figure 5.

Crude mean pain scores at each visit among participants in Protocol 127 (Panel a), and estimated treatment effects (active – placebo) and corresponding 95% confidence intervals for pregabalin 300/600 mg/day (Panel b) using different methods for handling missing data. LOCF = Last observation carried forward; BOCF = Baseline observation carried forward; MAR = Missing at random; J2R = Jump to reference (control-based imputation).

Protocol 196

Figure 6.

Crude mean pain scores at each visit among participants in Protocol 196 (Panel a), and estimated treatment effects (active – placebo) and corresponding 95% confidence intervals for pregabalin 300 mg/day (Panel b) and pregabalin 300/600 mg/day (Panel c) using different methods for handling missing data. LOCF = Last observation carried forward; BOCF = Baseline observation carried forward; MAR = Missing at random; J2R = Jump to reference (control-based imputation).

Table 1.

Summary of pregabalin clinical trial protocols

Protocol	Pain Condition	Total Sample Size	Pregabalin Dosages (mg/day)	Follow-up Visits (Weeks)
014	DPN	246	0, 150, 600	0, 2, 4, 6
029	DPN	337	0, 75, 300, 600	0, 1, 3, 5
040	DPN	254	0, 600 *	0, 1, 2, 5, 8
131	DPN	146	0, 300	0, 1, 3, 5, 8
030	PHN	255	0, 75, 150	0, 1, 3, 5
045	PHN	238	0, 150, 300	0, 1, 3, 5, 8
127	PHN	173	0, 300/600 †	0, 1, 3, 5, 8
196	PHN	368	0, 150, 300, 300/600 †	0, 1, 4, 8, 13
032	CLBP	253	0, 150, 600	0, 1, 3, 5, 7
104	CLBP	406	0, 300, 450, 600	0, 1, 3, 5, 8
031	Osteoarthritis	296	0, 300, 600	0, 1, 3, 6, 9, 12
105	Fibromyalgia	529	0, 150, 300, 450	0, 1, 3, 5, 8

DPN: diabetic peripheral neuropathy; PHN: postherpetic neuralgia; CLBP: chronic low back pain

* An arm with amitriptyline 75 mg/day was also included in Protocol 040

† Subjects in this arm received either 300 mg/day or 600 mg/day depending on their creatinine clearance at baseline

Table 2.

Reasons for subject dropout in the pregabalin clinical trial protocols

Protocol	Adverse Event	Lack of Efficacy	Lack of Compliance	Lost to Follow-up	Withdrawal of Consent	Unrelated	Ineligible	Patient Withdrawn In Error	Protocol Violation	Unclear
014 (n = 167)	11 (6.6%)	2 (1.2%)		3 (1.8%)		2 (1.2%)	2 (1.2%)			6 (3.6%)
029 (n = 260)	16 (6.2%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)				21 (8.1%)
040 (n = 167)	13 (7.8%)	13 (7.8%)	4 (2.4%)			1 (0.6%)			1 (0.6%)	11 (6.6%)
131 (n = 146)	10 (6.8%)	4 (2.7%)	2 (1.4%)	1 (0.7%)		1 (0.7%)				11 (7.5%)
030 (n = 88)	6 (6.8%)	2 (2.3%)		1 (1.1%)						4 (4.5%)
045 (n = 157)	21 (13.4%)	8 (5.1%)	3 (1.9%)	1 (0.6%)		2 (1.3%)				1 (0.6%)
127 (n = 173)	32 (18.5%)	6 (3.5%)	2 (1.2%)		1 (0.6%)					
196 (n = 281)	40 (14.2%)	41 (14.6%)	2 (0.7%)	1 (0.4%)	6 (2.1%)	2 (0.7%)		5 (1.8%)	3 (1.1%)	17 (6.0%)
032 (n = 172)	32 (18.6%)	6 (3.5%)	7 (4.1%)	2 (1.2%)	1 (0.6%)	1 (0.6%)				8 (4.7%)
104 (n = 301)	41 (13.6%)	18 (6.0%)	13 (4.3%)	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (1.7%)			17 (5.6%)
031 (n = 296)	71 (24.0%)	16 (5.4%)	8 (2.7%)	2 (0.7%)	1 (0.3%)	2 (0.7%)				17 (5.6%)
105 (n = 266)	20 (7.5%)	24 (9.0%)	6 (2.3%)	3 (1.1%)	4 (1.5%)					15 (5.6%)
Total (n = 2474)	313 (12.7%)	142 (5.7%)	48 (1.9%)	17 (0.7%)	17 (0.7%)	15 (0.6%)	7 (0.3%)	5 (0.2%)	4 (0.2%)	128 (5.2%)

Only the placebo arm and active treatment arms with a pregabalin dosage of 300 mg/day or 600 mg/day are included

Table 3.

Percentages of subjects dropping out in the pregabalin clinical trial protocols

	Placebo		300 mg/day		600 mg/day	
Protocol	Non-AE	AE	Non-AE	AE	Non-AE	AE
014	11.8%	4.7%	Not applicable		6.1%	8.5%
029	11.3%	3.1%	12.3%	3.7%	8.5%	12.2%
040	19.8%	4.9%	Not applicable		16.3%	10.5%
131	17.1%	2.9%	9.2%	10.5%	Not applicable	
030	8.0%	6.8%	Not applicable		Not applicable	
045	14.8%	9.9%	3.9%	17.1%	Not applicable	
127 [†]	7.1%	4.8%	Not applicable		3.4%	31.5%
196 [†]	37.6%	6.5%	27.6%	15.3%	16.7%	21.1%
032	13.3%	4.4%	Not applicable		15.9%	34.1%
104	26.2%	7.8%	18.2%	15.2%	15.2%	18.2%
031	18.5%	10.9%	11.1%	25.3%	17.1%	34.3%
105	24.2%	7.6%	14.9%	7.5%	Not applicable	

Only the placebo arm and active treatment arms with a pregabalin dosage of 300 mg/day or 600 mg/day are included

[†]Subjects in the 600 mg/day arm for this protocol received either 300 mg/day or 600 mg/day depending on their creatinine clearance at baseline