pmc painmanagement collaboratory

Supporting Research in Pain Management for Veterans and Military Service Members

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Prevention of Missing Data in Pragmatic Clinical Trials of Non-pharmacologic Interventions for Pain Management

Abstract

Missing data in trials of pain management are common as dropout rates tend to be high[1,2]. In clinical trials, missing data can reduce power and bias study conclusions. Pragmatic trials differ from explanatory trials in that they aim to follow-up participants no more than would be the case in usual care [3]. In fact, trials at the most extreme end of the pragmatic spectrum have no follow-up contact with participants and obtain outcome data from existing sources such as the electronic health record (EHR). Participants in trials at this end of the spectrum may not even know they are in a trial. While approaches are available for analysis in the presence of missing data, plans for prevention of missing data are particularly vital for pragmatic pain trials. This white paper discusses some approaches used in pragmatic trials from the Pain Management Collaboratory (PMC[3]) to limit the extent of missing data.

Problem Statement

Missing data in trials of pain management are common as dropout rates tend to be high[1,2]. In the presence of missing data, due to unverifiable assumptions about the mechanism by which missing data occurred, definitive analysis such as intent to treat to determine the impact of assignment to the intervention is not possible. Given the inability to confirm assumptions about the missing data mechanism required by any analysis, it is imperative to identify preventive measures that limit the occurrence of missing data.

Background

At the least, missing data in a trial can reduce power. At worst, missing data may bias comparisons of interventions and lead to incorrect (biased) conclusions. While methods have been developed for analysis in the presence of missing data, the result of any statistical analysis relies on the *unverifiable* ***assumptions*** concerning the relation between the unobserved data and the reasons they are missing[4]. Consequently, conclusions drawn from clinical trials with missing data can vary depending on the assumptions made and the analytic method chosen[5].

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In their guidelines on the handling of missing data in clinical trials[6], the National Research Council (NRC) recommends an analysis that makes full use of information on all randomized participants and is based on plausible assumptions about the nature of the missing data. However, recognizing the limitations of any analysis in the presence of missing data, the NRC additionally states[7]:

The assumption that analysis methods can compensate for such missing data are not justified, so aspects of trial design that limit the likelihood of missing data should be an important objective.

Methods for the prevention of missing data during the design, planning and execution of clinical trials have been reported[1,5,8]. However, approaches specific to the prevention of missing data in pragmatic trials of pain management are not available. Missing data in trials of pain management are common as dropout rates tend to be high[1,2]. Pragmatic trials differ from explanatory trials in that they aim to follow-up participants no more than would be the case in usual care [3]. This paper discusses some of the approaches to limit the occurrence of missing data used in the 11 trials of non-pharmacologic interventions in the PMC[3,9]. While this is not an exhaustive list of preventive measures, it highlights some of the more common approaches for pragmatic trials of pain.

Examples from PMC[3] Trials

Eight of the 11 PMC[3] trials identified methods targeting the prevention of missing data. These included the following:

- **Distinguish discontinuation of the intervention from study withdrawal** – Despite a participants' discontinuation of the intervention, effort should be made by the investigators to continue data collection (most importantly for the primary outcome). Informed consent procedures should clearly allow for this distinction and explain the importance of completing the assessments to potential participants.
- **Reduction of participant burden** – Participant burden is a common reason for dropout. Limiting the number of research-specific assessments (particularly in-person visits) and the duration of assessment are important design considerations. Several of the studies in the PMC[3] reduce participant burden by collecting data passively from the electronic health record (EHR). For those indicating withdrawal because of burden during the study, offering a reduced assessment schedule (i.e. perhaps just to collect the primary outcome) may attenuate the amount of missing data. For studies that collect data both from the EHR and interviews or questionnaires, informed consent and withdrawal procedures should distinguish interview or questionnaire withdrawal from the withdrawal of data collection from the EHR.

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- **Design/select outcomes with less missingness** – While collection of outcomes using the EHR may reduce participant burden, outcomes must be chosen or designed to assure reliable and unbiased assessment. For instance, the VA measures pain intensity as a 5th vital sign recorded in the EHR. This is an attractive potential outcome for a pragmatic study conducted in a VA setting given its integration into regular clinical practice and low additional participant burden. However, given its irregular assessment (i.e. only when a participant accesses the VA healthcare system and at the discretion of the clinician) its utility in a rigorous clinical trial is questionable. If using the EHR, pilot work will be necessary to assure the data is collected with satisfactory completeness at the intervals required of the study. As an example of outcome selection, DP11 uses a sub-sampling strategy. In this strategy, EHR data collection of primary outcomes are performed without informed consent on the full sample and a sub-sample is consented to be surveyed for the primary outcomes as well as additional secondary outcomes by phone.
- **Flexible data collection** – Deciding on the ideal level of standardization for data collection is important for each study. In some cases, very narrow windows are required for scheduled assessments. In others, the windows can be extended to improve completeness. Offering alternative modes of data collection might improve completeness. For example, the COPES ExTRA study (DP 15) conducts telephone interviews or mails surveys when participants do not complete planned automated Interactive Voice Response (IVR) assessments. Another example is the VERDICT study (DP 13) that is collecting participant-reported data through electronic data capture using REDCap. Participants in this study also have the option of a telephone interview if they do not complete the electronic questionnaires.
- **Acceptance of concomitant medications/interventions or rescue interventions** – Dropout in studies of chronic pain may occur from the lack of benefit of the intervention for a participant. Acceptance of concomitant medications/interventions and/or provision of rescue therapies may alleviate this obstacle. Of course, tracking the utilization of these additional therapies is essential. The PMC[3] Phenotype Workgroup developed a standardized assessment for tracking types, intensity, frequency and duration of non-pharmacological pain therapies.
- **Integrated prompts for research data collection in clinical assessments** – Prompts can be used to remind patients, clinicians, etc. to perform research tasks and provide research data. The VERDICT trial (DP13) of low vs high dose chiropractic care initially proposed using MyHealtheVet, a patient-facing portal to the EHR, to schedule chiropractic visits and perform assessments. MyHealtheVet allows study personnel to set up automated and ad-hoc messages via text, email or phone to remind participants of visits or assessments. DP14 uses a web-based platform called Military Orthopaedics Tracking Injuries and Outcomes Network (MOTION) to

identify patients who meet eligibility criteria and to prompt clinicians to collect patient-reported outcomes and intervention data for musculoskeletal conditions. MOTION can send electronic reminders and surveys to patients at regular time intervals outside of a healthcare visit and track completion rates. DP11 will be providing reports to clinical personnel as reminders to contact patients for primary outcome follow-up assessments and will monitor EHR for appropriate timing of outcome assessments.

- **Enhancement of study engagement** – Methods to encourage study retention can reduce the potential for study dropout. Staggered remuneration for participation, provision of reminders for visits/assessment, and newsletters with study updates are common practice. For example, the LAMP study (DP19) provides a welcome packet at enrollment with low-cost useful study-branded items and a website that delivers general information to all participants. VERDICT (DP13) participants receive a $25 gift card for each completed assessment (given in-person at the baseline visit and then mailed for the other assessments; a total of 6 assessments). Participants who are randomly selected to do interviews also receive a $25 gift card after the interview (mailed).
- **Monitor missing data** – Once the study has commenced, it is important to monitor the completeness of the follow-up and take active measures to reduce missing data. Regular checks of compliance with forms and completeness of data items (particularly for the primary and secondary outcomes) should be a trial requirement and these processes should be performed as early as possible to allow time for remediation. If available, rates of missing data can be compared with previous studies and with the anticipated attrition rate used in sample size/power calculations. A process for the resolution of these edit checks by sites or study staff should be described in the manual of operations. Routine report cards of overall study and site-specific data completeness can be shared with individual sites to improve performance. For example, VERDICT (DP13) prepares and discusses reports of centrally collected patient reported outcomes at weekly project meetings. DP11 will have regular contact/phone meetings with clinical teams at sites to discuss how recruitment, intervention delivery and outcome assessments are going, to be able to address issues that arise specifically due to the pragmatic nature of the trial. Study-wide or site-specific problems may trigger protocol modifications or address workflow or staff alterations.

Recommendations

1. All trials should have a missing data plan as part of their protocol. In addition to discussing analytic strategies for accommodating missing data, the plan should identify the specific strategies the trial will employ to prevent missing data.
2. Prevention strategies should be considered for the design, planning and execution phases of a trial.

Conclusion

Given the inability to confirm assumptions about missing data required by any analysis, it is imperative to identify preventive measures that limit the occurrence of missing data, in pragmatic clinical trials of pain where dropout is inevitable.

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