

PRACTICAL TIPS FOR SURGICAL RESEARCH

How to optimize participant retention and complete follow-up in surgical research

Manraj Kaur, MSc*
Sheila Sprague, PhD**
Teegan Ignacy, BSc, PharmD
(Cand)[†]
Achilles Thoma, MD, MSc**
Mohit Bhandari, MD, PhD**
Forough Farrokhyar, MPhil,
PhD**[†]

From the *Department of Surgery,
[†]Department of Clinical Epidemiology
and Biostatistics, McMaster University,
Hamilton, Ont.; and the †Leslie Dan Fac-
ulty of Pharmacy, University of Toronto,
Toronto, Ont.

Accepted for publication
Mar 28, 2014

Correspondence to:
F. Farrokhyar
Department of Surgery
McMaster University
39 Charlton Ave. E, Room 107
Hamilton ON L8N 1Y3
farrokh@mcmaster.ca

DOI: 10.1503/cjs.006314

Ensuring all participants attend the follow-up visits is crucial to achieving an unbiased assessment of treatment effect. An important consideration is the feasibility and willingness of patients to participate in the trial and comply with the requirements mandated in the trial protocol. Patients' refusal to participate may result in low enrolment and limit the generalizability of the findings.¹ Patients agreeing to participate but failing to complete the trial (i.e., those deemed lost to follow-up or those who withdraw from the trial) present a major threat to the internal and the external validity of the trial. This threat to validity is most prominent when there are systematic differences between the patients who do not complete the trial in the treatment groups.² Akl and colleagues^{3,4} assessed the reporting and handling of loss to follow-up and its potential impact on the estimates of treatment effect in randomized controlled trials (RCTs) in highly ranked medical journals. The authors concluded that plausible assumptions of outcomes for the participants who were lost to follow-up could change the interpretation of findings. Therefore, surgical researchers should anticipate and strive to limit the loss to follow-up at the stage of trial design, during the trial conduct and at the time of data analysis.

OBJECTIVES

This article discusses the methodological impact of loss to follow-up on the internal and external validity of a trial and provides practical methods of obtaining complete follow-up in RCTs. We focus on the importance of minimizing and handling loss to follow-up in surgical trials. The reader will appreciate why minimizing loss to follow-up is important.

METHODOLOGICAL IMPACT OF LOSS TO FOLLOW-UP

The purpose of randomization in surgical trials is to balance the known and unknown prognostic factors at the initiation of the trial to provide an unbiased estimation of the treatment effect at the conclusion of the trial.² If the prognostic factors are balanced across the treatment groups and the treatment has no effect, the number of participants experiencing the target outcome will be comparable among the groups. If the treatment has an effect and the between-group differences in outcome of interest are ascertained, the investigators can confidently relate the differences to the novel treatment.⁵

Failure to account for all included participants at the end of the trial presents a major threat to the internal validity of the trial.^{2,6,7} In reality, when conducting large RCTs, some participants are inevitably lost to follow-up. There are various reasons for participants not attending follow-up appointments — participants may have died, experienced the outcome of interest or ill health, or have satisfactory outcomes. Follow-up may be lost for practical and legitimate reasons; participants may change their names, addresses and phone numbers, or personal circumstances may prevent them from completing the trial.

At other times, participants may simply be noncompliant and/or lose interest in the trial.

Participants who do not attend follow-up visits often have different baseline characteristics than those who do attend. Previous research has demonstrated that losses to follow-up are higher when no treatment is needed after surgery, especially when a longer follow-up period with no specific treatment is required.^{2,8} The threats to credibility and validity of the trial are most prominent when there are systematic differences between comparison groups in the losses to follow-up or when there is attrition bias (i.e., withdrawals from the study).^{2,6,7} The differential loss to follow-up is greater when concomitant interventions, such as rehabilitation or physiotherapy, are required postsurgery for 1 group, but not the other.^{2,8} When comparing a surgical treatment to a medical treatment, there is a significant chance of attrition owing to participants who fail to attend follow-up visits or withdraw from the trial in the medical group owing to dissatisfaction with their treatment option.⁸ Michaels and colleagues⁸ conducted an RCT to compare varicose vein surgery with conservative treatment for uncomplicated varicose veins. At 1-year follow-up, there was significant attrition owing to patients failing to attend follow-up visits or withdrawing from the trial. Further attempts to contact patients revealed that none in the surgical group withdrew owing to dissatisfaction with surgery, while in the conservative group most withdrawals were among patients who decided to undergo surgery. In fact, from our own experience, loss to follow-up is less of a problem in oncology trials than trauma trials. Different regions have reported contradictory data on participant retention in cancer trials. Judson and colleagues⁹ asked participants receiving chemotherapy at a tertiary cancer centre who had access to a home computer and prior email experience to self-report 7 symptomatic toxicities via the Internet, and they reported a monthly compliance rate of 83% without attrition until the month before a patient's death. On the other hand, Sharma¹⁰ reported a very high loss to follow-up for cancer patients in India and suggested that methods used to minimize loss to follow-up in developed countries may not be practical in countries like India. Regardless of the reason, the participants who drop out or who are lost to follow-up represent an atypical subgroup.^{6,7,11} The systematic differences between the discontinuers and continuers threaten the credibility as well as the generalizability of the findings.²

Many losses to follow-up particularly increase the possibility of a type-2 error (i.e., false-negative result), undermining the study power.^{6,7,12} A few patients lost in a 1000-patient trial may not threaten power, but a few hundred patients lost in a trial that size most likely will threaten power. In such a scenario, the probability that an effective intervention will be abandoned is not unrealistic.¹³ If an investigator strives to maintain the sample size, a high attrition rate can result in inflating the sample size and

extending the length of the trial. This can create a delay in the roll-out of a potentially effective intervention, while increasing the cost and workload of the trial itself.¹³

METHODS OF OPTIMIZING PARTICIPANT RETENTION AT DIFFERENT STAGES OF A TRIAL

The best strategy to limit loss to follow-up is prevention. To prevent loss to follow-up, we propose a more beneficial framework: segmenting the trials into consecutive stages. These stages not only represent the natural progression of a trial, but also the unique opportunity for minimizing participant attrition.

Stage 1: planning the trial

The planning stage is typically characterized by procurement of funding, establishment of the research team, selection of the clinical site, finalization of the trial protocol and case report forms, and development of the recruitment and retention strategy.¹ The study protocol defines the population and the eligibility criteria, clinical setting (walk-in clinics v. hospital) and source of eligible patients.⁶ The rationale behind choosing a particular eligibility criterion must be well defined. Eligibility criteria that are too lax might give results that are not specific to the disease under consideration, and criteria that are extremely stringent will result in slow recruitment and will not be generalizable to the patient population¹.

Once the eligibility criteria are ascertained and the recruitment strategy developed, the investigators at each participating clinical site, in the case of a multicentre trial, may retrospectively estimate the possible recruitment rate^{13,14} (i.e., the number of patients that will be eligible for the study divided by the number of patients screened). This estimation can be accomplished by applying the eligibility criteria to patient charts at the centre retrospectively for 3 months or by conducting prospective sham enrolments.¹⁴ The research ethics board office will need to approve the method. In prospective sham enrolments, every study centre completes a patient screening form for all potential participants and ascertains the interest in participation for the eligible patients if such a trial were to exist.¹⁴ This method assists the investigators to obtain a real world sense of the time it will take to reach the sample size, resolve eligibility issues and recruit more study centres if required.

The compliance rate is an important factor to be considered during the trial planning stage. For example, a patient may be unable to refuse participation outright, possibly fearing a poor relationship with the investigator, but may eventually drop out later in the treatment protocol (passive resistance).¹⁵ Several studies have demonstrated a direct association between certain patient characteristics, such as race, age and history of substance abuse, and higher

rates of participant attrition. While excluding these patients may make the study less generalizable, including the patients poses a potential risk to the completeness of the data. Including a “run-in” or “wash-out” period in clinical trials^{11,16} in which patients complete 1–2 visits before inclusion in the study, can help differentiate compliant from noncompliant participants. Further, during the run-in period, collecting feedback on the intervention burden (i.e., issues related to the intervention that may affect adherence and compliance, such as injections or multiple trips to hospital) can assist to further resolve the noncompliance issue. Some tips to alleviate the intervention or patient burden and optimize participant retention are presented in Box 1.

Conducting a pilot or feasibility study on a smaller number of patients will assist in troubleshooting the operational aspects of a protocol for a full-scale trial. Issues such as participant recruitment and retention strategies, efficient use of resources (time and funds), intervention burden, choice of patient-important outcomes, appropriate length of follow-up and attrition likelihood, could be resolved with a feasibility study.^{13,17} In addition, duration, frequency and timing of the follow-up visits could be determined and maintained as close to “standard care” at the pilot stage. Furthermore, pilot studies are helpful in determining the minimal clinically important difference and calculating the sample size for the full-scale trial.

Because the estimated sample size represents the minimum allowable numbers, factors such as anticipated losses to follow-up, dropouts, drop-ins and noncompliance should be accounted for in sample size calculations to ensure an adequate level of power throughout the trial.¹⁸

Stage 2: initiation of the trial

At this stage, the eligible participants (those who meet all of the inclusion criteria and none of the exclusion criteria) will undergo screening for enrolment in the trial. These

eligible participants, depending on the design of the study, could be recruited sequentially or as a cluster. The “supremo” of this stage is the person, usually the onsite research coordinator, who will make the first contact with the patient about the trial. The goal is to assess the patients’ interest in the trial and provide detailed information on the trial if the patient is interested. The amount of effort, time commitment and associated risks should be discussed in detail. The screening process can vary from asking a few questions for some trials (e.g., Are you at least 18 years old? Do you read, write and understand English? Are you diabetic?) to conducting more detailed physical and laboratory examinations for others (e.g., prostate specific antigen testing, bone densitometry, magnetic resonance imaging). The time lag between the first contact, patient screening and the length of screening has been found to be proportional to the increased susceptibility of patients to drop out after enrolment.^{15,19} Patients who do not have a fixed address or who are going through a divorce or moving to another location, for example, should be handled with care for enrolment as it is highly probable that they will withdraw from the study. Any delay in completion of screening independent of the patient’s health and situation should alert the research personnel of the increased likelihood of attrition.¹⁵ Detailed characteristics of the patients screened and deemed eligible and those who agreed to participate as well as reasons for refusal to participate should be documented for reporting trial results according to the Consolidated Standards of Reporting Trials guidelines for early detection of selection bias and for generalizability of the study findings.²⁰

Once the patient is enrolled in the study, special consideration must be paid to establishing the relationship between the research coordinator and the participant. The research coordinator should be trained to collect the participant information in a culturally and sociodemographically sensitive manner. The standard set of information collected at this stage is provided in Box 2. For elderly patients, it is helpful to collect the contact information for their children or next of kin instead of collecting the address of an elderly spouse. A statement to this effect would have to be included in the informed consent form. If the patient is employed or owns a business, collecting information pertaining to the name of the employer/business, mailing address, phone number and website can also help in locating the patient. Additional age-specific strategies, like collecting Facebook or Twitter account details for younger patients can be used. More recently, trials in North America have resorted to collecting patients’ social insurance, drivers license and/or health card numbers,²¹ though ethics approval must be obtained and patient confidentiality must be protected at all times. Gathering this extra information takes only few minutes and may be vital to contacting a patient for future follow-up visits.

Box 1. Tips to optimize participant retention

Target-oriented data collection

- Collect only what is absolutely necessary to answer the research question.
- Prepare 2 sets of questions — 1 that is mandatory and 1 that can be waived in case it is not feasible for patients to complete.
- Alleviate the need for long-term follow-up by using proxy measures with earlier end points.
- Select questionnaires/procedures with lesser response time without compromising the result.

Make it convenient for the participant

- Complete questionnaires via telephone or send them in the mail.
- Email the questionnaires to the participant.
- Offer evening (after work hours) or weekend follow-up visits.
- Systematically organize trial procedures so that the patient moves quickly through the visits.
- Remain sensitive to wait times.
- Conduct the follow-up visits at a location convenient for the patient if possible (i.e., close to home/workplace/school).

Stage 3: conduct of the trial

During this stage, enrolment and follow-up visits are ongoing and it is expected that the logistical aspects of the trial be optimized. The most commonly advocated aspect in this stage is to maintain contact with the study participants. The research coordinator can contact the participants to confirm their full names (in case the name changed after to marriage or deed poll),²¹ mailing addresses, telephone numbers and names of general practitioners. This regular contact will assume greater importance if the time points or follow-up visits are spaced out. A tracking system (manual or electronic) can be used to improve scheduling of patients' visits. Logbooks, automated email reminders, or computer software capable of ongoing updating and monitoring can be used. Computerized systems, though helpful, can be expensive and time-consuming to establish, but as more and more practices incorporate electronic health records, the use of computer-driven tracking and reminder systems will become more prevalent. Sharma¹⁰ has noted that the methods used to retain participation in Western countries may not apply to developing countries where treatment resources are not easily available. The study reported that a prepaid postcard system increased the follow-up rate from 33% to 69% among cancer patients.

A detailed report of the up-to-date status of every participant must be maintained. For instance, if a participant reports that her husband is scheduled for surgery at the time of her next follow-up visit, this should be noted and attempts should be made to accommodate this conflict.

Box 2. Standard information collected at the baseline visit*

- First and last name
- Age
- Sex
- Date of birth
- Residential address
- Phone number (cellular: _____ home: _____)
- Email address
- Best time to contact
- Marital status
- Employment status
- Education level
- Income level

Additional information that could be collected (avoid misspellings)

- Next of kin name, address, telephone number
- Business name, address, telephone number and website
- General practitioner name, address and telephone number
- Facebook/MySpace/Twitter account name
- Drivers license number
- Health card number
- Social insurance number
- Passport number/ permanent residency (or green card) number
- Participant photograph

*Information presented in this box must be collected in accordance with ethical principles, and patient confidentiality must be ensured at all times.

The use of answering machines and toll-free numbers in addition to responding to patient phone calls in a timely manner will aid in this process.²² Details on patients who were missed or lost to follow-up and the related reasons should be documented. This information will be handy particularly if there is a change in research personnel. When a research coordinator leaves, temporarily or permanently, it can disrupt the trial substantially and hamper the trust and relationship established between participants and the coordinator. An agreement between the research staff and the principal investigator to provide 4 weeks' notice before leaving the study allows adequate time to ensure that a replacement is found and may help avoid the possibility of damaging the participant-coordinator relationship.²³ The training of new recruits by the senior staff is mandated apart from ensuring a long-term commitment from the coordinators.

The investigators should frequently review enrolment and follow-up rates across each of the participating clinical sites. If the enrolment is progressing at a rate slower than expected, a decision to involve more clinical sites can be contemplated. Regular meetings (quarterly or biannually), newsletters or emails from the principal investigators might be particularly opportune in maintaining contact with the participating sites. Collins and colleagues²⁴ have proposed some strategies for salvaging a study when the recruitment is very slow. These strategies are to increase intake or the recruitment period (least likely to lead to bias) if slightly underestimated, to find other sources of study patients (e.g., community screening, media strategies, mass mailing), to increase the number of participating sites (impractical if it will take a long time to obtain ethics approval and start recruitment) and to replace the sites experiencing no or very slow recruitment. A "pay-for-performance" model¹⁴ in which sites are compensated based on enrolment and follow-up is recommended. Another proposed strategy is to relax the criteria for exclusion and include patients that were formerly excluded; however, the resulting problem with this option is that the study population will now be different from that entered previously. Another strategy is re-evaluation of the calculated sample size that most affects the integrity, credibility and decisiveness of the trial. A decision to recalculate sample size without compromising the clinically important differences, significance level and study power may be considered. Some of the planned subgroup analyses built into the sample size can be forfeited, or the study end points might have to be redefined.²⁴ These approaches will reduce the confidence in the findings if the compromises are too great. Finally, the optimal decision might be early termination of the trial. Regardless of the wasted time, efforts and funds, this may be the only sensible decision if the recruitment is so slow that the required sample size cannot be achieved in a timely manner.²⁴ Additional and practical strategies that can be used in certain population are described in Box 3.

Stage 4: trial close-out

Once the last follow-up visit of the last enrolled patient is completed, the data are analyzed for patterns of missing data, and an effort is made to locate patients who were lost to follow-up. Contacting the patients' next of kin, alternate contacts and/or employers should be the first steps to locate the patients. Hospital or electronic medical records, if available and up-to-date, are also useful to determine the patients' current location and health status. Apart from this, publicly available resources, such as telephone directories, obituaries and death records, can be found via online searches. There are several information brokers who provide paid service and help in tracking a patient²¹; however, use of such a service will depend on the trial budget and the stringency of privacy laws that apply in the trial location. Free websites, such as www.canadamissing.ca and www.findthemissing.org/en, also offer information.

Box 3. Strategies for preventing loss to follow-up in certain populations

Pediatric patients

- Provide study-specific educational material to parents and children.³⁹
- Provide education and training manual to study staff (physicians, research coordinator, nurses, etc.) with tips for educating and motivating the patients.³⁹
- Organize semiannual or annual parties, gift toys, t-shirts, coffee mugs, pens, key chains, calendars, story books, and hats with study logo for the participants.
- Give certificate of appreciation to participants and thank you notes to parents.^{23, 39}
- Give a "passport" containing a picture of the child. The child's height and weight at each appointment are recorded in the passport, as well as the dates of scheduled food diary completion and activity.
- Update the passport by inserting a new photograph of the child at each clinic visit or annually. Take pictures of the entire family and post on a display board with a different theme each year.²³
- Respond promptly to questions and problems. Provide feedback on participation, and ask patients what motivates them.²³
- Provide babysitting services for guest children.²³
- Keep staff consistent.

Working population

- Schedule suitable visit times — early morning/evenings/weekends.
- Schedule visits close to work or home.
- Make arrangements for child care during visits.

Elderly patients

- Involve the patient's family/caregivers.
- Allow rest between interviews/tests as needed.
- Arrange transportation to the visit location or reimburse the transportation costs.
- Keep the visit short (< 2 h).
- Provide opportunity for building social support by means of organized group educational sessions.
- Keep in touch, schedule appointments in advance and send reminders.

Patients with psychological issues

- Employ well-trained research personnel. Allow time to bond with the patient.
- Involve a family member or caregiver.

Racial minorities

- Employ well-trained research personnel; the same racial background is an advantage.
- Involve family members and translators if required.

Searching for surnames on Facebook or Twitter, enquiring in local churches and other searches can be performed to locate the patient. The reality of clinical research is that despite the best efforts of the research team, some patients will be lost to follow-up. They might have, for example, moved to a different location, been a part of natural calamity, gone to prison or died. Hence, it is crucial that every resource is used to identify the missing participants. Once they are deemed missing, different strategies to handle the missing data at the stage of data analysis should be considered. This is often anticipated and taken into account a priori at the stage of trial design. Tips to minimize loss to follow-up are provided in Box 4.

METHODS OF HANDLING AND REPORTING MISSING DATA

As mentioned, missing data can have a profound impact on the results of research studies by introducing bias and skewing the interpretation of the results. If the missing data are substantial, the power, credibility and validity of a research study can be substantially compromised. While some missing data are inevitable, these can be addressed using a variety of statistical approaches. It has been reported that missing data in RCTs are often improperly

Box 4. Tips to minimize loss to follow-up in surgical trials

Stage 1. Planning of the trial

- Determine clear eligibility criteria.
- Identify the patient population and clinical setting.
- Involve motivated investigators with previous successful trial records.
- Hire and train committed research staff.
- Calculate the recruitment yield (retrospective/prospective with sham enrolment).
- Include a "run-in" or "wash-out" period to identify compliant patients.
- Pilot the study to assess intervention burden and straighten logistics of the study.

Stage 2. Initiation of the trial

- Keep the duration between screening and enrolment short.
- Establish a relationship between participant and research personnel.
- Collect additional information at the baseline visit.
- Maintain a log of all events.

Stage 3. Conduct of the trial

- Regularly update the demographic status of participant via phone or mail.
- Use a manual or online tracking system to schedule visits.
- Immediately follow up on missing or incomplete information.
- Provide participants with a study newsletter summarizing any updates or preliminary results, or simply send a letter of appreciation.
- Send patients birthday or anniversary cards.
- Keep an up-to-date record of all patients in the study, and document reasons for drop-outs or exclusions.

Stage 4. Trial close-out

- Identify the loss to follow-up patients, and make an effort to locate them.
- Make the most optimal statistical adjustments.

Multicentre/international trials⁴⁰

- Have well-designed and repeated training sessions.
- Employ research personnel to coordinate the trial and answer the questions at each site.
- Arrange quarterly reliability checks.
- Organize a centralized data management and monitoring system.

addressed.²⁵ This can be problematic, as evidence from RCTs is important for adequately evaluating interventions and forming the basis of evidence-based surgery. Once a patient is lost to follow-up, there are several means by which missing data can be handled. To decide how to handle the missing data, it is beneficial to know the reason why data are missing. Data could be missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR).²⁶ Data that are MCAR occur if the probability of missing data is the same for all participants and is not related to the values of that variable or any other variable in the data set²⁷ (e.g., in a patient who had bariatric surgery, the missing value to the question asking about the participant's weight was not related to the patient's weight or to the patient's sex). Data that are missing owing to malfunctioning equipment, to data entry errors, or to the patient missing his/her follow-up visit because of traffic, for example, would be considered MCAR. Data that are MAR occur when the probability of missing data for a variable is not related to the values of that variable but rather to other variables in the data set (e.g., missing data on surgical wait times are unrelated to the wait times but are related to the hospital where the surgery is performed). Finally, data that are MNAR occur when the probability of missing data for a variable is related to the values of that variable but not related to other variables in the data set (e.g., a patient with hypertension misses her/his postoperative follow-up visit because of abdominal pain; in this situation, the missingness relates to the abdominal pain on the day of the postoperative visit but not to hypertension). Prior to conducting the statistical analyses to address missing data, it is important to consider the possible causes for the missing data and determine if they are MCAR, MAR or MNAR. There are different approaches to handle the missing data, including deletion, weighting, single imputation and multiple imputations.

The deletion method assumes that the missing data are MCAR and deletes cases with missing values. There are 2 approaches. Listwise or casewise deletion excludes all cases with missing data for any of the variables in the data set for all statistical analyses.^{28,29} The reduced sample size may lead to a decrease in statistical power of the study and increase type-II error rates.³⁰ Nonetheless, this issue can usually be overcome with a larger sample size.³⁰ With missing data that are not MCAR, the deletion method can lead to biased results, such as insufficient standard errors and too-large or too-small regression coefficients.^{27,30} The pairwise deletion approach involves deleting the cases with missing data for each analysis and leads to different samples sizes for different parts of the statistical analysis; this approach is not recommended.²⁹ Weighting deletes the case with missing data but weights the cases with complete data to compensate for the cases with missing data. For example, if 1 case with complete data has very similar

characteristics to 4 cases with missing data, the case with complete data will be weighted by 4 to supplement the data for the cases with missing information.²⁷ Patricia²⁷ stated that "weighting decreases the variation because multiple identical values are replacing the missing values." Weighting reduces the bias that arises by case deletion methods but makes standard error calculation quite cumbersome.^{26,27}

Single imputation aims to generate data sets that are complete. Mean imputation involves replacing the missing data of a variable with the observed mean of all the available data for that variable.²⁹ Hot-deck imputation assumes no difference between cases with complete and incomplete data and matches the cases with missing data to those with similar characteristics and imputes the known values.²⁷ Finally, regression analysis (i.e. linear regression or stochastic regression) is another way of dealing with missing data by imputing complete case information.²⁷ Although single imputation is easy to use, it can be problematic because the uncertainty inherent in missing values is not taken into account. The imputed values are treated as if they were true, which overstates precision.²⁷

Last observation carried forward (LOCF) applies to repeated measures in longitudinal studies and is commonly used to deal with dropouts. It replaces the missing data with the measured data from the patient's last follow-up visit. The flaw of this method is distorted calculation of effect size, which leads to wrong inferences and false conclusions unless the proportion of missing data is too small to affect inferences.³¹ When there are missing data on binary outcome measure, a common sensitivity analysis is to explore best and worst case scenarios by replacing missing values once with good outcomes and another time with bad outcomes.³² The disadvantage is that imputing all missing values as either good or bad is a strong assumption and can give a wide range of estimates of the treatment effect.³²

Multiple imputation is considered the most optimal method as it addresses the problem with a single imputation approach because it preserves the uncertainty inherent in missing data.^{33,34} There are several assumptions that are made with multiple imputations. The missing data are assumed to be MAR.³⁵ For example, if a patient is likely to miss follow-up appointments because of some medical condition on the day of the appointment, then it is unlikely to justify the plausibility of an MAR assumption.³² Other assumptions are that the imputation model should reflect the intended model for the final analysis³⁵ and should take into account other variables in the data set and their associations with the missing data.³⁵ Multiple imputation involves the following 3 steps: randomly generate multiple data sets; analyze the data sets individually; and combine the results from the multiple data set analyses to produce a single set of parameter estimates, standard errors and test statistics.^{27,33,34} It is an advantageous approach as it can maintain sample size and thus statistical power for the study.

Transparency in the reporting of findings is essential, and Sterne and colleagues³² have provided guidelines for reporting the details of analysis potentially affected by missing data. In summary, the authors encourage researchers to report the number of missing values for each variable of interest; provide a flow chart with number of dropouts and patients lost to follow-up as well as the reason if possible; include a table comparing the baseline characteristics and outcomes of interest between participants with complete and incomplete data if substantial; describe the details of methods used to impute the missing data (i.e., the details of multiple imputation methods, modelling, included variables and used software) and the assumptions made to justify the use of that method (i.e., MAR); and provide results from analyses of the original and complete data set for comparison and discuss the differences.

ECONOMIC ASPECTS OF PATIENT ATTRITION

The budget for clinical trials could include compensating patients, staff, centres and referring institutes, with or without public campaigns. In lieu of available funding, 2 approaches might be adopted: the first is to start with the available budget and then determine what it can purchase in terms of recruitment and retention of participants, and the second is to set up a budget on a per-patient basis by calculating approximate recruitment costs to offset the research coordinator time on the trial. One strategy might be to contact the researchers from similar previous trials or to search the literature to deduce a reasonable cost for each recruitment.³⁶ Laboratory tests, dropouts, compliance, office supplies, computer-related costs, travel expenses and advertising campaigns are some of the considerations that should be factored into the budget planning.

Commonly, patients are offered compensation in the form of cash, gift cards or parking passes, for example, to reimburse them for their time and research-related expenses. How much and when to compensate have been a matter of debate for past decade.³⁷ Some researchers suggest that providing compensation to participants who complete the trial might put an undue pressure on the participants who will then participate passively.³⁷ Ultimately, the decision to compensate lies in the hands of the investigator and the budget approved for the study. The compensation should not be so low that it barely compensates the patients for their time or so unreasonably high that it is not ethically acceptable.³⁸

CONCLUSION

Participant retention and complete follow-up increases the integrity and credibility of a research study. It optimizes the internal and external validity of the study find-

ings. The possibilities of loss to follow-up should be anticipated and accounted for at the stage of planning a trial. Strategies should be used a priori at different stages — from design to trial close-out — to enhance participant retention and complete follow-up and to optimally handle the missed follow-up data in order to draw definitive conclusions.

Acknowledgements: The authors thank Dyda Dao for her contribution in gathering and summarizing the literature for selected sections of the manuscript.

Competing interests and Funding: The authors have no conflicts of interest to disclose. No funding was received for this article. M. Bhandari is funded, in part, by a Canada Research Chair, McMaster University.

Contributors: All authors contributed substantially to writing and revising and to the conception and design of this article and approved the final version for publication.

References

1. Thoma A, Farrokhyar F, McKnight L, et al. Practical tips for surgical research: how to optimize patient recruitment. *Can J Surg* 2010; 53:205-10.
2. Farrokhyar F, Karanicolas PJ, Thoma A, et al. Randomized controlled trials of surgical interventions. *Ann Surg* 2010;251:409-16.
3. Akl EA, Briel M, You JJ, et al. LOST to follow-up information in trials (LOST-IT): a protocol on the potential impact. *Trials* 2009; 10:40.
4. Akl EA, Briel M, You JJ, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. *BMJ* 2012;344:e2809.
5. Montori VM, Guyatt GH. Intention-to-treat principle. *CMAJ* 2001;165:1339-41.
6. Altman DG. Statistics and ethics in medical research. Collecting and screening data. *BMJ* 1980;281:1399-401.
7. Altman DG. Statistics and ethics in medical research: III How large a sample? *BMJ* 1980;281:1336-8.
8. Michaels JA, Brazier JE, Campbell WB, et al. Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. *Br J Surg*. 2006;93:175-81.
9. Judson TJ, Bennett AV, Rogak LJ, et al. Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. *J Clin Oncol* 2013;31:2580-5.
10. Sharma D. Postcard system helps follow up lost patients. *Lancet Oncology* 2000;1:7.
11. Vervolgyi E, Kromp M, Skipka G, et al. Reporting of loss to follow-up information in randomised controlled trials with time-to-event outcomes: a literature survey. *BMC Med Res Methodol* 2011;11:130.
12. Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. *JAMA* 1994; 272:122-4.
13. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010;10:1.
14. Sibai T, Carlisle H, Tornetta P III. The darker side of randomized trials: recruitment challenges. *J Bone Joint Surg Am* 2012;94 (Suppl 1):49-55.
15. Siddiqi AE, Sikorskii A, Given CW, et al. Early participant attrition from clinical trials: role of trial design and logistics. *Clin Trials* 2008; 5:328-35.
16. Hulley SB. *Designing clinical research*. Philadelphia (PA): Lippincott Williams & Wilkins; 2007.
17. Loscalzo J. Pilot trials in clinical research: Of what value are they? *Circulation* 2009;119:1694-6.

18. Farrokhyar F, Reddy D, Poolman RW, et al. Why perform a priori sample size calculation? *Can J Surg* 2013 Jun;56:207-13.
19. Sikorskii A, Wyatt GK, Siddiqi AE, et al. Recruitment and early retention of women with advanced breast cancer in a complementary and alternative medicine trial. *Evid Based Complement Alternat Med* 2011;2011:734517.
20. Sliker FJ, Kompanje EJ, Murray GD, et al. Importance of screening logs in clinical trials for severe traumatic brain injury. *Neurosurgery* 2008;62:1321-8; discussion 8-9.
21. Biant L, Eswaramoorthy V, Field R. How to find patients who are 'lost to follow-up.' *Bulletin of the Royal College of Surgeons of England*. 2010;92:98-101.
22. Marmor JK, Oliveria SA, Donahue RP, et al. Factors encouraging cohort maintenance in a longitudinal study. *J Clin Epidemiol* 1991; 44:531-5.
23. Spilker B, Cramer JA. *Patient recruitment in clinical trials*. New York (NY): Raven Press; 1992.
24. Collins JF, Williford WO, Weiss DG, et al. Planning patient recruitment: fantasy and reality. *Stat Med* 1984;3:435-43. Published online 1984/10/01.
25. Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clin Trials* 2004;1:368-76.
26. Little RJA, Rubin DB. *Statistical analysis with missing data*. New York (NY): J. Wiley & Sons; 1987.
27. Patrician PA. Multiple imputation for missing data. *Res Nurs Health* 2002;25:76-84.
28. Buhi ER, Goodson P, Neilands TB. Out of sight, not out of mind: strategies for handling missing data. *Am J Health Behav* 2008;32:83-92.
29. McKnight JL. *Missing data: a gentle introduction*. New York (NY): The Guilford Press; 2007.
30. Acock AC. Working with missing values. *J Marriage Fam* 2005; 67:1012-28.
31. Molnar FJ, Hutton B, Fergusson D. Does analysis using "last observation carried forward" introduce bias in dementia research? *CMAJ* 2008;179:751-3.
32. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
33. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991;10:585-98.
34. Groenwold RH, Donders AR, Roes KC, et al. Dealing with missing outcome data in randomized trials and observational studies. *Am J Epidemiol* 2012;175:210-7.
35. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8:3-15.
36. Patel MX, Doku V, Tennakoon L. Challenges in recruitment of research participants. *Adv Psychiatr Treat* 2003;9:229-38.
37. Gul RB, Ali PA. Clinical trials: the challenge of recruitment and retention of participants. *J Clin Nurs* 2010;19:227-33.
38. Gross D, Fogg L. Clinical trials in the 21st century: the case for participant-centered research. *Res Nurs Health* 2001;24:530-9.

How you can get involved in the CMA!

The CMA is committed to providing leadership for physicians and promoting the highest standard of health and health care for Canadians. To strengthen the association and be truly representative of all Canadian physicians the CMA needs to hear from members interested in serving in elected positions and on appointed committees and advisory groups. The CMA structure comprises both governing bodies and advisory bodies either elected by General Council or appointed by the CMA Board of Directors. The Board of Directors — elected by General Council — has provincial/territorial, resident and student representation, is responsible for the overall operation of the CMA and reports to General Council on issues of governance.

CMA committees advise the Board of Directors and make recommendations on specific issues of concern to physicians and the public. Five core committees mainly consist of regional, resident and student representation while other statutory and special committees and task forces consist of individuals with interest and expertise in subject-specific fields. Positions on one or more of these committees may become available in the coming year.

For further information on how you can get involved please go to <https://www.cma.ca/en/Pages/get-involved-in-cma.aspx>, or contact

Cherise Araujo
Corporate and Governance Services
Canadian Medical Association
1867 Alta Vista Drive, Ottawa ON K1G 5W8
Fax 613 526-7570, Tel 800 663-7336 x1949
cherise.araujo@cma.ca

By getting involved, you will have an opportunity to make a difference.

We hope to hear from you!

ASSOCIATION
MÉDICALE
CANADIENNE  CANADIAN
MEDICAL
ASSOCIATION