A commentary by Douglas R. Dirschl, MD,
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Predicting and Preventing Loss to Follow-up of Adult Trauma Patients in Randomized Controlled Trials

An Example from the FLOW Trial

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Background: High loss-to-follow-up rates are a risk in even the most rigorously designed randomized controlled trials (RCTs). Consequently, predicting and preventing loss to follow-up are important methodological considerations. We hypothesized that certain baseline characteristics are associated with a greater likelihood of patients being lost to follow-up. Our primary objective was to determine which baseline characteristics are associated with loss to follow-up within 12 months after an open fracture in adult patients participating in the Fluid Lavage of Open Wounds (FLOW) trial. We also present strategies to reduce loss to follow-up in trauma trials.

Methods: Data for this study were derived from the FLOW trial, a funded trial in which payments to clinical sites were tied to participant retention. We conducted a binary logistic regression analysis with loss to follow-up as the dependent variable to determine participant characteristics associated with a higher risk of loss to follow-up.

Results: Complete data were available for 2,381 of 2,447 participants. One hundred and sixty-three participants (6.7%) were lost to follow-up. Participants who received treatment in the U.S. were more likely to be lost to follow-up than those who received treatment in other countries (odds ratio [OR] = 3.56, 95% confidence interval [CI]: 2.46 to 5.17, $p < 0.001$). Male sex (OR = 1.75, 95% CI: 1.15 to 2.67, $p = 0.009$), current smoking (OR = 1.82, 95% CI: 1.28 to 2.58, $p = 0.001$), high-risk alcohol consumption (OR = 1.88, 95% CI: 1.16 to 3.05, $p = 0.010$), and an age of <30 years (OR = 2.16, 95% CI: 1.19 to 3.95, $p = 0.012$) all significantly increased the odds of a patient being lost to follow-up. Conversely, participants who had sustained polytrauma (OR = 0.52, 95% CI: 0.37 to 0.73, $p < 0.001$) or had a Gustilo-Anderson type-IIIa, B, or C fracture (OR = 0.60, 95% CI: 0.38 to 0.94, $p = 0.024$) had lower odds of being lost to follow-up.

Conclusions: Using a number of strategies, we were able to reduce the loss-to-follow-up rate to <7%. Males, current smokers, young participants, participants who consumed a high-risk amount of alcohol, and participants in the U.S. were more likely to be lost to follow-up even after these strategies had been employed; therefore, additional strategies should be developed to target these high-risk participants.

continued

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

Disclosure: The FLOW (Fluid Lavage of Open Wounds) trial was supported by research grants from the Canadian Institutes of Health Research (MCT-93173), U.S. Army Institute of Surgical Research Orthopedic Trauma Research Program (W81XWH-08-1-0473), U.S. Army Institute of Surgical Research Peer Reviewed Orthopedic Research Program (W81XWH-12-1-0530), and Association Internationale pour l'Ostéosynthèse Dynamique. Stryker donated Surgilav irrigators for the trial for clinical sites in Asia. Zimmer provided the Pulsavac irrigator at a reduced cost to selected clinical sites in North America. Triad Medical donated castile soap; castile soap from Apicare was purchased at full cost. Ms. Madden is funded by a Canadian Institutes of Health Research (CIHR) Doctoral award (GSD-134929). Dr. Bhandari is funded, in part, by a Canada Research Chair. No donor or funder had a role in the design or conduct of the study, the collection or analyses of the data, or the preparation of the manuscript. On the **Disclosure of Potential Conflicts of Interest** forms, which are provided with the online version of the article, one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work (<http://links.lww.com/JBJS/D155>).

Clinical Relevance: This study highlights an important need to develop additional strategies to minimize loss to follow-up, including targeted participant-retention strategies. Male sex, an age of <30 years, current smoking, high-risk alcohol consumption, and treatment in a developed country with a predominantly privately funded health-care system increased the likelihood of participants being lost to follow-up. Therefore, strategies should be targeted to these participants. Use of the planning and prevention strategies outlined in the current study can minimize loss to follow-up in orthopaedic trials.

High loss-to-follow-up rates are a risk in even the most rigorously designed randomized controlled trials (RCTs). When a large number of participants are lost to follow-up the study power is reduced and substantial bias can occur when the participants who are lost to follow-up differ from those who remain in the study in terms of outcome variables¹.

In the past, researchers have typically considered a 20% loss to follow-up to be the threshold for an increased risk of bias due to loss to follow-up², but this threshold was not evidence-based. More recently, Zelle et al.³ determined that, in more than one-quarter of 50 simulated orthopaedic trials, the results changed from significant to nonsignificant when the authors simulated a loss of follow-up of 20%. This indicates that the 20% threshold may not be strict enough to mitigate the risk of bias from loss to follow-up. The authors recommended that researchers aim to achieve a follow-up rate of >80%³. Strategies that have previously been used to reduce loss to follow-up from clinical trials include regularly searching for alternative contact information, searching death registries and other national registries, setting follow-up-rate goals, calling at different hours of the day, leaving voice messages, and repeated contact⁴⁻⁷.

While RCTs in all surgical specialties are susceptible to loss to follow-up, orthopaedic trials have a particularly poor record in terms of both reporting loss-to-follow-up rates^{8,9} and achieving adequate follow-up rates¹⁰. Consequently, minimizing loss to follow-up has become an important methodological consideration in trauma trials¹¹. However, even when participant-retention strategies are employed, it is likely that some participants will still be lost to follow-up. Young age, male sex, smoking, substance abuse, an isolated orthopaedic injury, and a lack of insurance were linked to loss to follow-up of trauma patients from an orthopaedic practice¹⁰. However, that study was limited by the fact that it was a retrospective review conducted at only 1 center in the U.S. and included a small number of participants (n = 309). A systematic review of loss-to-follow-up rates in orthopaedic trials demonstrated that studies conducted in the U.S. had higher rates and that trauma trials did not have significantly worse rates than those in other orthopaedic subspecialties⁹. The pooled loss-to-follow-up rate in this systematic review was 10.4%.

We hypothesize that not all trauma trial participants have the same risk of being lost to follow-up and that certain baseline characteristics are associated with a greater likelihood of being lost to follow-up. The objectives of this study were (1) to determine which baseline characteristics were associated with loss to follow-up within 12 months after an open fracture

in an adult patient participating in the Fluid Lavage of Open Wounds (FLOW) trial, in which general strategies for reducing loss to follow-up were implemented; and (2) to describe the strategies that we used in the FLOW trial to achieve a lower-than-average loss-to-follow-up rate. Identifying which trauma trial participants are at an increased risk of being lost to follow-up would allow future research to focus on developing and evaluating retention strategies aimed specifically at participants identified as having a high risk of being lost to follow-up. Our experiences with reducing loss to follow-up in the FLOW trial may be beneficial to other investigators wishing to reduce their loss-to-follow-up rates as well.

Materials and Methods

Data for this study were derived from the FLOW trial, a large multicenter initiative that was conducted at 41 clinical sites in Canada, the U.S., Norway, Australia, and India (ClinicalTrials.gov: NCT00788398). The FLOW trial was a 2 × 3 factorial RCT evaluating the impact of irrigation solution (soap versus saline solution) and irrigation pressure (high versus low versus very low) on the risk of a reoperation to promote wound or bone healing or to treat infection in adult patients with an open fracture of an extremity. The FLOW trial recruited 2,447 participants, who were scheduled to be followed for 12 months with follow-up appointments at 1, 2, and 6 weeks and 3, 6, 9, and 12 months postsurgery. A detailed description of the trial methodology¹² and results¹³ have been published elsewhere.

Definition of Loss to Follow-up in the FLOW Trial

In the FLOW trial, participants were considered lost to follow-up when they had been withdrawn from the study before their final 12-month follow-up visit because they could not be located by study personnel. Participants who were withdrawn early for other reasons such as death or because they withdrew their consent were not classified as lost to follow-up because these reasons for withdrawal were deemed to be beyond the study team's control. We determined that a participant's withdrawal of consent was beyond our control because we had already implemented strategies to minimize factors that might cause a participant to withdraw consent; these strategies included allowing participants who felt overburdened by the questionnaires to fill out fewer questionnaires and allowing telephone visits for those who did not want to return to the clinic. However, it should be noted that, since good clinical practice guidelines¹⁴ and the Canadian Tri-Council Policy Statement¹⁵ dictate that research participants must be free to withdraw consent at any time, strategies aimed at reducing early withdrawal must be carefully considered to ensure that they are not coercive.

Strategies to Minimize Loss to Follow-up in the FLOW Trial

We implemented an intensive strategy to minimize loss to follow-up in the FLOW trial, as shown in Table I. Some main features of the strategy included designing the follow-up schedule to align with standard-of-care visits, selection of a primary outcome that could be obtained without an in-person visit, selection of clinical sites with experienced research coordinators, efforts to be flexible with scheduling and not overburden participants, multiple attempts to contact participants, and routine verification of contact

TABLE I Strategies to Prevent Loss to Follow-up in the FLOW Trial

Strategy	
Design phase	<ul style="list-style-type: none"> ● Design the follow-up schedule to align with typical standard-of-care visits to reduce the site and patient burden ● Select a primary outcome that can be easily obtained over the telephone or from clinic records, if possible ● Design the study to strike a balance between collecting enough data and not overburdening patients ● Obtain funding to offset costs of implementing intensive strategies to prevent loss to follow-up, if possible ● Select participating clinical sites with experienced research coordinators who can implement procedures to reduce loss to follow-up
At baseline	
Methods-center level	<ul style="list-style-type: none"> ● When training personnel at sites, ensure that they are aware of the importance of loss to follow-up and its consequences for the trial
Site level	<ul style="list-style-type: none"> ● Exclude patients who are expected to be lost to follow-up (e.g., those with no fixed address, plans to move out of town, or an intellectual disability with no support) ● Collect >1 piece of contact information for the patient and a family member or friend ● Ensure that the patients understand the follow-up schedule and what is expected of them during the trial ● Ask the patients for consent to access their medical records
During trial	
Methods-center level	<ul style="list-style-type: none"> ● Send monthly newsletters that include reminders about loss to follow-up and helpful tips about preventing it ● Allow telephone visits and/or mailed questionnaires for at least the primary outcome data, if possible ● Allow flexibility in the follow-up schedule. An “out-of-window” visit is better than a missed visit ● Tie payments to sites to completion of follow-up
Site level	<ul style="list-style-type: none"> ● Routinely verify patients’ contact information ● Allow flexibility in scheduling clinic visits for patient convenience, if possible ● Log attempts to contact patients and review the logs regularly ● Between visits, remind patients about upcoming visits
For patients lost, or at high risk of being lost, to follow-up	
Methods-center level	<ul style="list-style-type: none"> ● Follow up with sites regularly about patients lost to follow-up throughout the trial ● Whenever a patient has been lost to follow-up, place queries on his/her data for the duration of the trial as a reminder to sites
Site level	<ul style="list-style-type: none"> ● Attempt to reach alternate contacts ● Try to contact patients at different times of day (e.g., during the day and in the evening) ● Try to contact patients on the weekend ● Repeatedly search for updated patient information and continue to try disconnected telephone numbers ● Search local telephone books ● Search local obituaries and death registries, if possible ● If the patient feels overburdened by questionnaires, prioritize which outcome measures are the most important and reduce the questionnaire burden ● If you have consent, check the patient’s medical record for adverse events, hospitalizations, etc.

information. When a participant had missed visits and was at risk of being lost to follow-up, we implemented specific procedures, including searching medical records for new admissions, searching obituaries and death registries, attempting to contact participants in the evening and on weekends,

and reducing the questionnaire burden. The methods center also placed a query on the data of participants who were presumed lost to follow-up as a reminder to continue to attempt to locate them. Participants were not compensated for attending follow-up visits, and none of their medical costs

TABLE II Participant Characteristics by Loss-to-Follow-up Status

Characteristic	No. (%)*		
	Not Lost to Follow-up (N = 2,284)	Lost to Follow-up (N = 163)	Total (N = 2,447)
Mean age $\pm$ SD (yr)	45.1 $\pm$ 17.8	38.6 $\pm$ 15.9	44.7 $\pm$ 17.8
Sex			
Male	1,552 (68.0)	128 (78.5)	1,680 (68.7)
Female	713 (31.2)	35 (21.5)	748 (30.6)
Missing	19 (0.8)	0 (0.0)	19 (0.8)
Current smoker			
Yes	696 (30.5)	81 (49.7)	777 (31.8)
No	1,549 (67.8)	79 (48.5)	1,628 (66.5)
Missing	39 (1.7)	3 (1.8)	42 (1.7)
IV drug abuse			
Yes	30 (1.3)	1 (0.6)	31 (1.3)
No	2,214 (96.9)	157 (96.3)	2,371 (96.9)
Missing	40 (1.8)	5 (3.1)	45 (1.8)
High-risk alcohol consumption			
Yes	234 (10.2)	26 (16.0)	260 (10.6)
No	1,993 (87.3)	133 (81.6)	2,126 (86.9)
Missing	57 (2.5)	4 (2.5)	61 (2.5)
Work-related injury			
Yes	331 (14.5)	18 (11.0)	349 (14.3)
No	1,925 (84.3)	145 (89.0)	2,070 (84.6)
Missing	28 (1.2)	0 (0.0)	28 (1.1)
Employment status			
Unemployed/disabled	277 (12.1)	36 (22.1)	313 (12.8)
Retired/student/employed/homemaker	1,970 (86.3)	125 (76.7)	2,095 (85.6)
Missing	37 (1.6)	2 (1.2)	39 (1.6)
Health-care system			
Industrialized/publicly funded	1,369 (59.9)	58 (35.6)	1,427 (58.3)
Industrialized/privately funded	687 (30.1)	93 (57.1)	780 (31.9)
Industrializing/privately funded	228 (10.0)	12 (7.4)	240 (9.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Location of fracture			
Upper extremity	705 (30.9)	53 (32.5)	758 (31.0)
Lower extremity	1,560 (68.3)	110 (67.5)	1,670 (68.2)
Missing	19 (0.8)	0 (0.0)	19 (0.8)
Polytrauma			
Yes	1,380 (60.4)	72 (44.2)	1,452 (59.3)
No	886 (38.8)	91 (55.8)	977 (39.9)
Missing	18 (0.8)	0 (0.0)	18 (0.7)
Gustilo-Anderson fracture type			
I	585 (25.6)	54 (33.1)	639 (26.1)
II	842 (36.9)	57 (35.0)	899 (36.7)
IIIA/B/C	829 (36.3)	52 (31.9)	881 (36.0)
Missing	28 (1.2)	0 (0.0)	28 (1.1)

*For all variables except age.

were covered by the study. Clinical sites were paid an average of \$500 CAD outside of the U.S. and \$750 USD within the U.S. for complete follow-up of participants. Payments were issued in installments and tied to data submission to incentivize sites to maximize follow-up.

Statistical Methods

Demographics

The characteristics of the participants who were lost to follow-up are reported separately from those of participants who were not. Means and standard deviations (SDs) are presented for continuous variables, and frequencies and percentages are presented for categorical variables. All analyses were conducted using SPSS version-23.0 software (IBM).

Primary Analysis

We conducted a binary logistic regression analysis with loss to follow-up as the dependent variable¹⁶. In the binary logic regression model, we included independent variables (i.e., age category, sex, smoking status, intravenous [IV] drug abuse, high-risk alcohol consumption, work-related injury, employment status, location of fracture, polytrauma, Gustilo-Anderson fracture type, and health-care system) selected on the basis of clinical relevance and previous research^{10,17-19}. We defined “high-risk alcohol consumption” as >7 drinks per week for women and >14 drinks per week for men according to National Institutes of Health (NIH) guidelines²⁰. Authors of previous studies have observed greater challenges with follow-up of trauma patients who are younger males^{18,19}. Because this greater challenge has also been reported for uninsured participants¹⁰, we hypothesized that participants who receive treatment in health-care systems that are not publicly funded (e.g., those in India and the U.S.) would be more likely to be lost to follow-up. We tested for interactions between key variables. We present results as odds ratios (ORs) with 95% confidence intervals (CIs) and associated p values. We assessed multicollinearity using the variance inflation factor for all variables included in the model. We decided a priori that variables with a variance inflation factor of ≥ 10 would be considered multicollinear and removed. Finally, we used leverage and deviance statistics to identify influential outliers. As there were few cases of missing data (<3%), we did not complete any statistical imputations.

Sensitivity Analysis

It was decided post hoc to conduct sensitivity analyses in which a binary logistic regression was conducted without influential outliers.

Results

Participant Characteristics

This study included 2,447 participants, and complete data were available for 2,381 (97.3%) of them. One hundred and sixty-three participants (6.7%) were lost to follow-up. Table II presents demographic and injury characteristics of the participants who were lost to follow-up, those who were not, and overall. Most participants were male (69%), and the mean age in the cohort was 45 years. Seven hundred and seventy-seven (32%) were current smokers, 31 (1.3%) reported IV drug abuse, and 260 (11%) reported high-risk alcohol consumption. Three hundred and forty-nine (14%) had a work-related injury. Most fractures (68%) were of the lower extremity, and most participants (59%) had several injuries.

Loss to Follow-up

The final model included the following variables: age category, sex, current smoking, high-risk alcohol consumption,

TABLE III Binary Logistic Regression Model for Loss to Follow-up*

Covariate	OR	95% CI	P Value
Age			
<30 yr	2.16	1.19-3.95	0.012
30-60 yr	1.31	0.72-2.37	0.371
>60 yr	—	—	—
Male	1.75	1.15-2.67	0.009
Current smoker	1.82	1.28-2.58	0.001
High-risk alcohol consumption	1.88	1.16-3.05	0.010
Polytrauma	0.52	0.37-0.73	<0.001
Gustilo-Anderson fracture type			
I	—	—	—
II	0.66	0.43-1.02	0.059
IIIA/B/C	0.60	0.38-0.94	0.024
Health-care system			
Industrialized/publicly funded	—	—	—
Industrialized/private funded	3.56	2.46-5.17	<0.001
Industrializing/private funded	0.92	0.49-1.91	0.966
*Adjusted for work-related injury, IV drug abuse, employment status, and fracture location (upper versus lower extremity).			

work-related injury, polytrauma, Gustilo-Anderson fracture type, IV drug abuse, employment status, fracture location, and type of health-care system in which the treatment was received (Table III). No variables were removed from the model as a result of multicollinearity as the variance inflation factor was low (<1.2) for all variables. There were 100 participants with moderate deviance values, and 8 with high leverage values.

The odds of being lost to follow-up were 3.56 times greater (95% CI: 2.46 to 5.17, $p < 0.001$) for participants who received treatment in the U.S. (i.e., in a predominantly privately funded health-care system) compared with those who received treatment in Canada, Europe, or Australia (which have publicly funded health-care systems). Receiving treatment in India (a developing country with a predominantly privately funded health-care system) was not significantly associated with loss to follow-up (OR = 0.92, 95% CI: 0.49 to 1.91, $p = 0.966$). Male sex (OR = 1.75, 95% CI: 1.15 to 2.67, $p = 0.009$), current smoking (OR = 1.82, 95% CI: 1.28 to 2.58, $p = 0.001$), high-risk alcohol consumption (OR = 1.88, 95% CI: 1.16 to 3.05, $p = 0.010$), and an age of <30 years (OR = 2.16, 95% CI: 1.19 to 3.95, $p = 0.012$) all significantly increased the odds of the participant being lost to follow-up. Conversely, participants who had sustained polytrauma (OR = 0.52, 95% CI: 0.37 to 0.73, $p < 0.001$) or a Gustilo-Anderson type-IIIA, B, or C fracture

(OR = 0.60, 95% CI: 0.38 to 0.94, $p = 0.024$) had lower odds of being lost to follow-up. None of the interaction terms were significant (all $p > 0.13$).

Sensitivity Analyses

The 108 participants identified as influential outliers were removed for binary logistic regression sensitivity analysis, which revealed findings similar to those of the primary analysis. The 1 exception was work-related injury, which the sensitivity analysis showed to be significantly associated with a decreased odds of being lost to follow-up (OR = 0.10, 95% CI: 0.01 to 0.81, $p = 0.031$).

Discussion

The results of this study show that the odds of being lost to follow-up are greater for participants who are male, currently smoke, are younger than the age of 30 years, consume a high-risk amount of alcohol, or received treatment in the U.S. Conversely, the odds of being lost to follow-up are lower for participants who sustained polytrauma or have a Gustilo-Anderson type-IIIa, B, or C fracture.

These findings are congruent with our past clinical experiences conducting trauma trials and also with previous research. For example, previous studies have shown that women tend to visit their doctors more than men²¹, which may suggest that they would be more likely to attend medical follow-up appointments. Smoking or consuming more alcoholic drinks may be indicative of poor health behavior attitudes, which may make participants less likely to return for medical follow-up appointments¹⁸. Participants who are older are less transient, and it may be easier for study personnel to locate them for follow-up visits. Participants with more severe injuries (a higher fracture type or polytrauma) may be more likely to return for study follow-up visits because of longer recovery times, need for ongoing care, and ongoing limitations to their functional abilities. Finally, participants who receive care in privately funded health-care systems may face barriers to attending scheduled follow-up visits if they are uninsured¹⁹. In agreement with our findings, a systematic review of loss-to-follow-up rates in orthopaedic trials also showed higher rates in trials completed in the U.S. than in those carried out in other countries⁹. We did not compensate participants for their time, travel costs, or medical care in this trial. Other studies have shown that providing monetary incentives to participants could improve follow-up rates, so this may be a strategy to consider in the future.

Work-related injury was not significantly associated with the odds of being lost to follow-up in the primary or secondary analysis. This finding is surprising given that treatment for work-related injuries is often covered through workplace insurance. Additionally, participants who are receiving Workers' Compensation have been shown to have worse outcomes after orthopaedic trauma^{17,22}. However, when the sensitivity analyses were conducted with the influential outliers removed, having a work-related injury was signifi-

cantly associated with lower odds of loss to follow-up. Future research should include an investigation of the association between work-related injuries and loss to follow-up given that our findings were inconclusive.

There have been previous studies on strategies to prevent loss to follow-up in clinical trials, several of which were conducted in an orthopaedic setting. A recent Cochrane review of 38 trials showed that 6 broad types of strategies have been used to improve retention in clinical trials, including incentives, communication strategies, new questionnaire strategies, behavioral/motivational strategies, case management, and methodological strategies²³. The only intervention that consistently improved retention was adding a monetary incentive²³. We were fortunate to be able to conduct the FLOW trial at sites with experienced research coordinators and to have funding to pay those sites for recruiting and following participants, thereby motivating them, through financial incentives, to follow participants for the full study period. However, a number of the strategies (e.g., all of the design-phase elements) that we implemented in the FLOW trial to reduce loss to follow-up (Table I) are not associated with any additional costs and some may help to improve efficiency and thus reduce costs. For example, conducting a telephone visit often takes less time than completing an in-clinic visit. Even strategies that have associated costs such as repeatedly contacting participants and calling them on weekends may be more cost-effective in the long term because preventing loss to follow-up helps to maintain study power, thereby mitigating the need to increase the study sample size. Future studies could focus on the cost-effectiveness of these strategies. It is also interesting to note that participants in the U.S. were more likely to be lost to follow-up even though U.S. sites were paid more per participant than those in other countries.

It is possible that retention strategies would be more effective if they were targeted toward participants at high risk of being lost to follow-up. The results of our study will allow clinical trial personnel at methods centers and at recruiting sites to be more aware of which participants are at risk of being lost to follow-up. We are unaware of any trials evaluating targeted strategies to enhance retention, which is an area of future study.

This study has several limitations. Given that we obtained our data from a completed RCT, we could include only previously collected variables in the model. For example, we hypothesized that socioeconomic status was an important predictor of loss to follow-up, but such data were not available. It is also likely that some of the variables collected in this study (e.g., substance abuse, employment, and smoking status) change over time and consequently so does the participant's risk of being lost to follow-up. While this is an important area of future research, assessing risk over time is beyond the scope of this study. It is also possible that, because these data came from a single trial, studies of different orthopaedic populations may reveal different risk

factors for loss to follow-up. However, the risk factors that we found in the current study are in line with hypothesized risk factors and previous research from other specialties^{10,17-19}, suggesting that our study is generalizable.

The strengths of this study include its large sample size, minimal amount of missing data (<3%), and diverse population. While we used data from a specific orthopaedic trial, the baseline variables included in the model represent data that are routinely collected in most trauma trials, enhancing the generalizability to other trauma trials.

The FLOW trial was a funded trial in which rigorous participant-retention strategies were employed in the design phase, at the start of the trial, and throughout the trial. However, despite these efforts, nearly 7% of the participants were lost to follow-up. This highlights an important need for additional strategies to minimize loss to follow-up, including targeted participant-retention strategies. Male sex, an age younger than 30 years, current smoking, high-risk alcohol consumption, and treatment in a developed country with a predominantly privately funded health-care system increased the likelihood of participants being lost to follow-up. Therefore, strategies should be targeted to these participants. Use of the planning and prevention strategies outlined in the current study can minimize loss to follow-up in orthopaedic trials.

Appendix

A list of the FLOW investigators is available with the online version of this article as a data supplement at [jbjs.org \(http://links.lww.com/JBJS/D156\)](http://links.lww.com/JBJS/D156). ■

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