Wound irrigation does not affect health-related quality of life after open fractures: results of a randomized controlled trial

S. Sprague,
B. Petrisor,
K. Jeray,
P. McKay,
D. Heels-Ansdell,
E. Schemitsch,
S. Liew,
G. Guyatt,
S. D. Walter,
M. Bhandari

On behalf of the FLOW Investigators. Please refer to the supplementary material for a full list of FLOW Investigators

■ S. Sprague, PhD, Assistant Professor PT, Department of Health Research Methods, Evidence and Impact (HEI), and Department of Surgery
■ B. Petrisor, MD, MSc, FRCSC, Orthopaedic Surgeon and Associate Professor, Department of Surgery
■ P. McKay, BSc, Research Program Manager, Department of Health Research Methods, Evidence and Impact (HEI)
■ D. Heels-Ansdell, MSc, Statistician and Assistant Professor PT, Department of Health Research Methods, Evidence and Impact (HEI)
■ G. Guyatt, MD, MSc, FRCPC, OC , Internist and Distinguished Professor, Department of Health Research Methods, Evidence and Impact (HEI)
■ S. D. Walter, PhD, FRSC, Professor, Department of Health Research Methods, Evidence and Impact (HEI)
■ M. Bhandari, MD, PhD, FRCSC, Orthopaedic Surgeon and Professor, Department of Health Research Methods, Evidence and Impact (HEI) and Department of Surgery
McMaster University, 293 Wellington Street North, Suite 110, Hamilton, Ontario L8L 8E7, Canada

■ K. Jeray, MD , Orthopaedic Surgeon and Clinical Professor, Department of Orthopedic Surgery Greenville Health System, 2nd Floor Support Tower, 701 Grove Road, Greenville, South Carolina 29605, USA

■ E. Schemitsch, MD, FRCSC , Orthopaedic Surgeon and Professor, Department of Surgery University of Western Ontario, 268 Grosvenor Street, Room E3-117, London, Ontario N6A 4V2, Canada

■ S. Liew, MBBS, FRACS, Orthopaedic Surgeon and Adjunct Clinical Associate Professor, Department of Surgery Monash University, Level 5, Block E, 246 Clayton Road, Clayton, Victoria 3168, Australia

Correspondence should be sent to S. Sprague; email: sprags@mcmaster.ca

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Aims
The Fluid Lavage in Open Fracture Wounds (FLOW) trial was a multicentre, blinded, randomized controlled trial that used a 2 × 3 factorial design to evaluate the effect of irrigation solution (soap *versus* normal saline) and irrigation pressure (very low *versus* low *versus* high) on health-related quality of life (HRQL) in patients with open fractures. In this study, we used this dataset to ascertain whether these factors affect whether HRQL returns to pre-injury levels at 12-months post-injury.

Patients and Methods
Participants completed the Short Form-12 (SF-12) and the EuroQol-5 Dimensions (EQ-5D) at baseline (pre-injury recall), at two and six weeks, and at three, six, nine and 12-months post-fracture. We calculated the Physical Component Score (PCS) and the Mental Component Score (MCS) of the SF-12 and the EQ-5D utility score, conducted an analysis using a multi-level generalized linear model, and compared differences between the baseline and 12-month scores.

Results
We found no clinically important differences between irrigating solutions or pressures for the SF-12 PCS, SF-12 MCS and EQ-5D. Irrespective of treatment, participants had not returned to their pre-injury function at 12-months for any of the three outcomes (p < 0.001).

Conclusion
Neither the composition of the irrigation solution nor irrigation pressure applied had an effect on HRQL. Irrespective of treatment, patients had not returned to their pre-injury HRQL at 12 months post-fracture.

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Open fractures are debilitating injuries frequently complicated by infection and problems associated with wound and fracture healing.[1-3] Their initial management includes thorough irrigation and debridement to remove debris and necrotic tissue.[4] There has been uncertainty over the choice of irrigating pressure and solution on both the rate of complications and patients' health-related quality of life (HRQL) after open fractures.[4-6] Used in conjunction with clinical outcomes, HRQL is highly relevant for the evaluation of fracture treatment and there has been an increase in its use in fracture trials.[7]

The Fluid Lavage in Open Fracture Wounds (FLOW) trial was a prospective, multicentre, randomized controlled trial that evaluated the effect of irrigation solution and pressure on rates of re-operation in 2447 adult patients.[3,8] Patients were randomized to one of three irrigating pressures: very-low pressure (1 psi to 2 psi), low pressure (5 psi to 10 psi), or high pressure (> 20 psi), and one of two irrigating solutions: 0.45% solution of castile soap (Castile Soap, Triad Medical, Hartland and Aplicare Inc., Meriden, Connecticut) or sterile normal saline alone. The primary outcome was a composite of re-operation, defined as surgery within 12 months of the initial procedure to treat infection at the operative site, management of wound-healing problems and promotion of bone healing. The assessment of HRQL for 12 months post-fracture was an *a priori* planned part of statistical analysis.[8] In the current study, we aimed to determine: the impact of the composition of the irrigation solution and pressure of its delivery on HRQL and if patient HRQL returns to pre-fracture levels by 12-months post-fracture.

Table I. Patient characteristics and surgical and peri-operative management

	HRQL cohort, n = 1860	Total FLOW cohort, n = 2447
Mean age (yrs) (SD)	45.4 (17.6), n = 1860	45.2 (17.8)*
Gender, n (%)		
Male	1273/1860 *(68.4)*	1680/2428 *(69.2)*
Female	587/1860 *(31.6)*	748/2428 *(30.8)*
Current smokers, n (%)	614/1857 *(33.1)*	777/2405 *(32.3)*
Work-related injuries, n (%)	295/1859 *(15.9)*	349/2419 *(14.4)*
Mechanism of injury, n (%)		
Motor vehicle accident (driver/passenger)	431/1860 *(23.2)*	613/2428 *(25.2)*
Motor vehicle accident (pedestrian)	197/1860 *(10.6)*	304/2428 *(12.5)*
Motorcycle accident	330/1860 *(17.7)*	414/2428 *(17.1)*
All-terrain vehicle accident	42/1860 *(2.3)*	47/2428 *(1.9)*
Crush injury	93/1860 *(5.0)*	116/2428 *(4.8)*
Fall from standing	202/1860 *(10.9)*	261/2428 *(10.7)*
Fall from height	352/1860 *(18.9)*	422/2428 *(17.4)*
Twist	25/1860 *(1.3)*	26/2428 *(1.1)*
Direct trauma (penetrating)	64/1860 *(3.4)*	74/2428 *(3.0)*
Direct trauma (blunt)	117/1860 *(6.3)*	141/2428 *(5.8)*
Explosion	1/1860 *(0.1)*	2/2428 *(0.1)*
Bicycle accident	5/1860 *(0.3)*	6/2428 *(0.2)*
Plane crash	1/1860 *(0.1)*	1/2428 *(0.04)*
Other	0/1860 *(0.0)*	1/2428 *(0.04)*
Major concomitant trauma, n (%)		
Head injury	103/1860 *(5.5)*	145/2429 *(6.0)*
Chest injury	124/1860 *(6.7)*	187/2429 *(7.7)*
Intra-abdominal injury	67/1860 *(3.6)*	95/2429 *(3.9)*
Any of the above	233/1860 *(12.5)*	328/2429 *(13.5)*
Gustilo Type, n (%)		
Type I	463/1857 *(24.9)*	639/2419 *(26.4)*
Type II	703/1857 *(37.9)*	899/2419 *(37.2)*
Type IIIA	526/1857 *(28.3)*	649/2419 *(26.8)*
Type IIIB	165/1857 *(8.9)*	232/2419 *(9.6)*
Location of fracture, n (%)		
Arm	554/1860 *(29.8)*	758/2428 *(31.2)*
Leg	1306/1860 *(70.2)*	1670/2428 *(68.8)*
Hours to first incision from injury, median (IQR)	10.0 (6.4 to 15.9), n = 1832	9.8 (6.4 to 15.9), n = 2374
Surgical preparation solution, n (%)		
Iodine or providone-iodine	1000/1852 *(54.0)*	1394/2413 *(57.8)*
Chlorhexidine	930/1852 *(50.2)*	1100/2413 *(45.6)*
Alcohol	294/1852 *(15.9)*	436/2413 *(18.1)*
Other	11/1852 *(0.6)*	14/2413 *(0.6)*
Definitive fixation, n (%)		
Intramedullary nail	635/1860 *(34.1)*	821/2422 *(33.9)*
External fixator	33/1860 *(1.8)*	59/2422 *(2.4)*
Plate	962/1860 *(51.7)*	1218/2422 *(50.3)*
Other internal fixation	221/1860 *(11.9)*	308/2422 *(12.7)*
Other	9/1860 *(0.5)*	16/2422 *(0.7)*

*the ages of four patients in the FLOW cohort were not known. Mean age was calculated with n = 2443
HRQL, health-related quality of life; FLOW, Fluid Lavage in Open Fracture Wounds; IQR, interquartile range

Patients and Methods

FLOW trial. Details of trial methodology and primary outcome results have previously been published.[3,8] Research Ethics Board approval for the trial was obtained at the co-ordinating centre (McMaster University) (REB: 08-268) and at each clinical site. The trial was prospectively registered at clinicaltrials.gov (NCT00788398).

HRQL. As a secondary outcome, patients enrolled in the FLOW study were asked to complete the 12-Item Short Form Health Survey (SF-12)[9] and the EuroQol-5 Dimensions Questionnaire (EQ-5D)[10] on recruitment to the trial (being asked to rate their pre-injury state), at two and six weeks, and at three, six, nine and 12-months post-injury.[11]

The SF-12 physical (PCS) and mental component scores (MCS) and EQ-5D index score were calculated according to the developers' recommendations. In our main analyses, we included patients where the SF-12 PCS, the SF-12 MCS or the EQ-5D score could be calculated for at least one follow-up visit between two weeks and 12 months.

Sample size. Sample size for the HRQL analysis was a factor in the development of the FLOW protocol.[8] We consid-

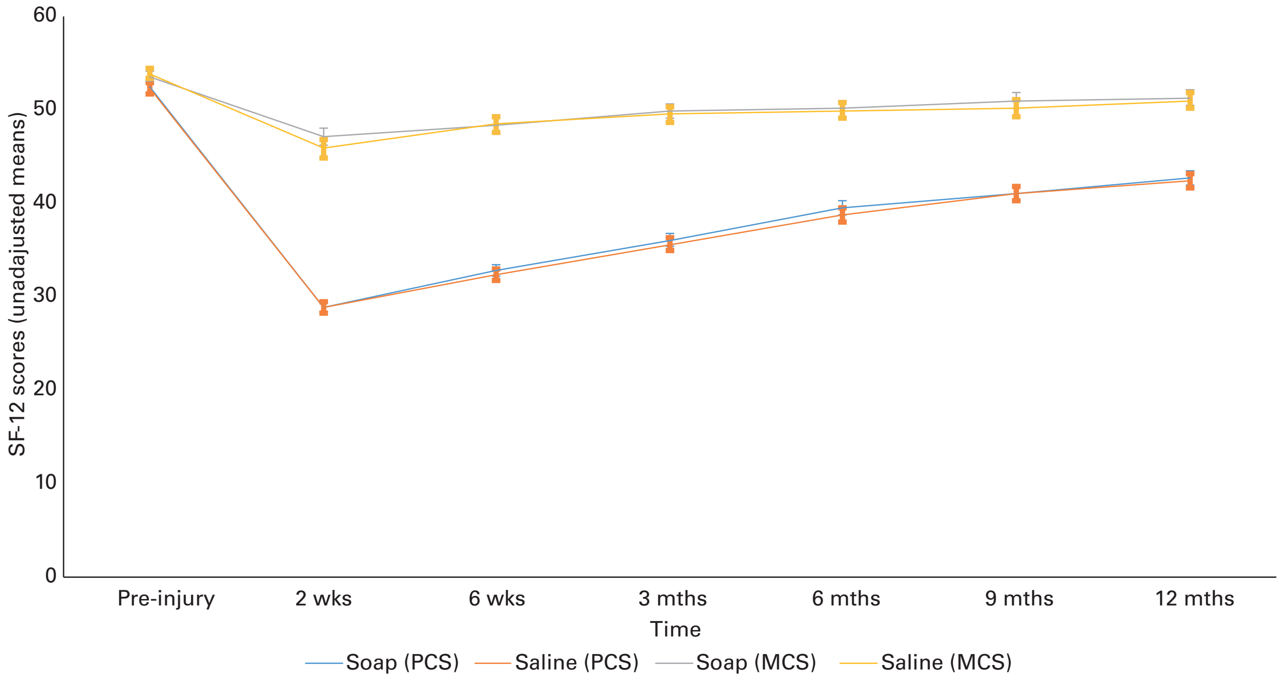

Fig. 1

Short Form (SF)-12 scores (physical component score (PCS) and mental component score (MCS)) over time by solution.

ered an important difference in SF-12 to correspond to a moderate effect as described by Cohen[12] and noted the minimally important difference in the SF-12 reported by Ware et al.[9] In both cases, the value is 0.5 SD, equivalent to a five-point difference in the score. Specifying an α-level of 0.01 and a β-level of 0.20 (study power = 0.80), we required a sample of at least 405 patients (135 in each of three groups).

Initial sample size calculations for the EQ-5D were based on previous literature suggesting that a 0.03 to 0.04 incremental change in the Health Utilities Index (HUI)[13] represents a patient-important difference,[14] and that the EQ-5D correlates well with the HUI.[15] We needed to recruit at least 329 patients in each of the three groups (α-level = 0.01, β = 0.20, difference = 0.04, σ = 0.15).

Data analysis. Our main analyses were based on multi-level generalized linear models, each comprising three levels (the clinical site, patient and time of HRQL assessment (i.e. visit)). We included the following independent variables: nature of the irrigation solution, pressure of irrigation, time point, baseline HRQL score and type of fracture (Gustilo type I/II vs. type III).[16]

Given that the FLOW trial evaluated both the pressure of and solution used for irrigation in the same patient population, we first ran the above model with an additional solution by a pressure interaction term, to identify any interaction between the two treatment factors. We planned *a priori* to remove from the model any interaction terms that were not significant.

Our final model for SF-12 PCS included the following independent variables: randomized solution, randomized pressure, time of HRQL assessment, pre-injury SF-12 PCS, fracture type and interaction of time of HRQL assessment by fracture type.

None of the interactions were significant in the analysis of the SF-12 MCS. The model therefore included: solution, pressure, time point, pre-injury SF-12 MCS and fracture type. The interaction of time point by fracture type was the only significant interaction term in the model for the EQ-5D. This model therefore included solution, pressure, time point, pre-injury EQ-5D score, fracture type and the interaction of time point by fracture type.

In addition to our main analysis, we performed an adjusted analysis that added factors to these models. These factors were: age, arm *versus* leg injury, postoperative fracture gap, initial method of internal fixation and severity of wound contamination.

We also conducted two *a priori* subgroup analyses for the SF-12 PCS, SF-12 MCS and EQ-5D scores, which were fracture type (Gustilo Type I or II *versus* Gustilo Type III);[16] and fracture location (arm *versus* leg).

The mean scores and SDs for the SF-12 PCS, SF-12 MCS and EQ-5D were plotted over time by solution treatment group and pressure treatment group. Mean differences between the baseline (pre-injury) SF-12 PCS, SF-12 MCS and EQ-5D scores and the corresponding 12-month scores were calculated and compared using paired *t*-tests. A p-value < 0.05 was considered statistically significant.

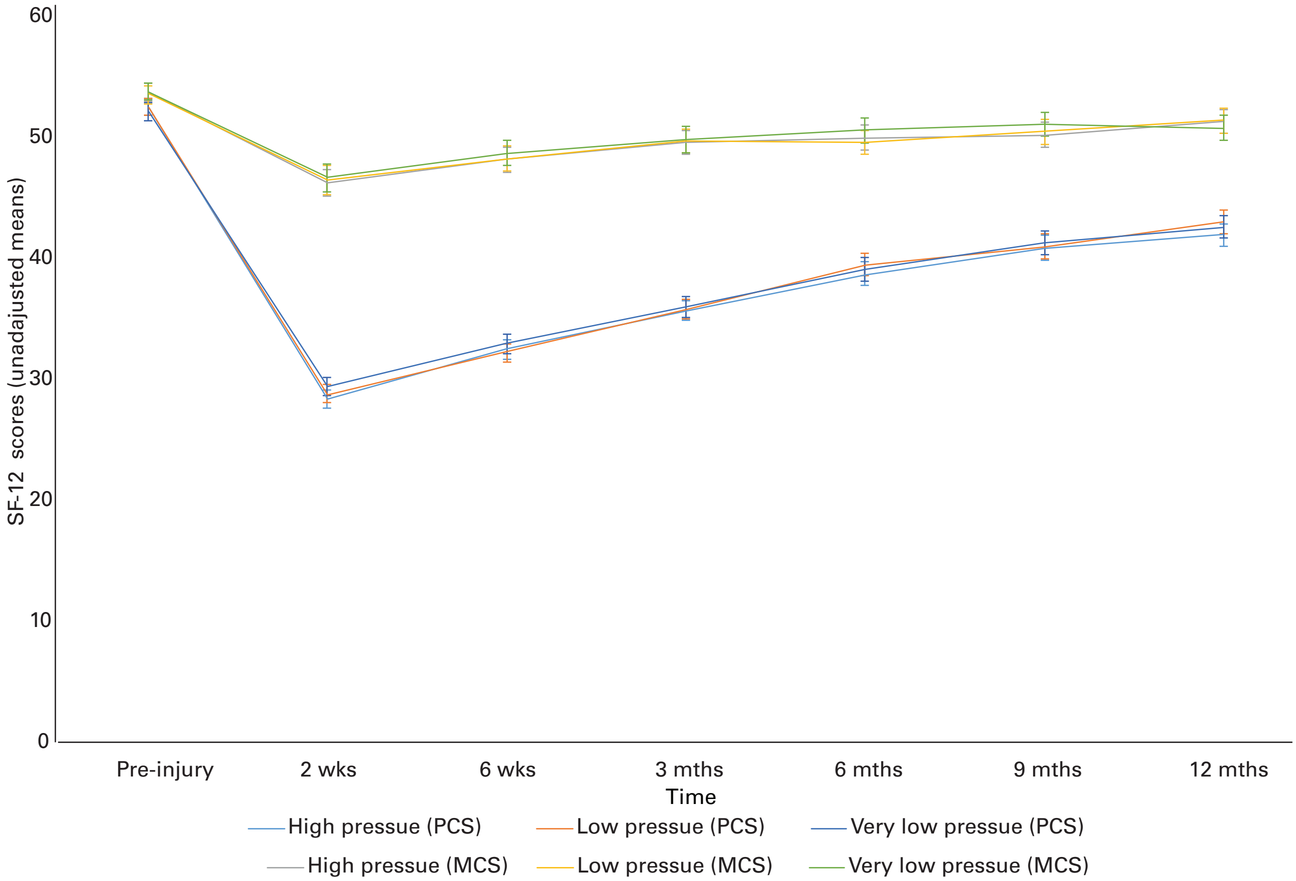

Fig. 2

Short Form (SF)-12 scores (physical component score (PCS) and mental component score (MCS)) over time by pressure.

Patient demographics. A total of 1860 patients were included, 1850 of whom completed the SF-12 and 1833 the EQ-5D. The patient demographics and injury characteristics are similar to the overall FLOW cohort (Table I).[3] Mean age was 45.4 years (SD 17.6) and most (n = 1273, 68.4%) were men.

Results

Most patients had a leg injury (n = 1306, 70.2%) and underwent definitive fixation with a plate (n = 962, 51.7%) or intramedullary nail (n = 635, 34.1%).

HRQL by irrigation pressures and solutions. We did not find any significant differences in SF-12 PCS, SF-12 MCS or EQ-5D utility scores between soap and saline or between the three irrigation pressure groups over the one-year follow-up period (Figs 1 to 3). Our adjusted analyses did not show any significant differences when compared with the main analyses, so unadjusted analyses are presented. We did not find subgroup effects on any outcome measure of fracture type or location.

In our analysis of the SF-12 PCS, we found a significant interaction (p = 0.032) between solution and pressure. As both variables had been included in the same model, we also included interaction terms between solution and time, and between pressure and time. In this model, the interaction was still significant (p = 0.032) but the interactions between time point and solution, and between time point and pressure were not significant (p = 0.88 and p = 0.54, respectively).

In order to evaluate the magnitude and nature of the interaction between pressure and solution, we examined the effect of solution within each level of pressure, and the effect of pressure within each level of solution (Table II). Since this interaction was an unexpected finding, we sought to objectively evaluate its credibility. We elected to adapt criteria that have previously been used to assess the credibility of a sub-group analysis[17] to determine if our observed interaction was believable. Based upon the application of these criteria, we determined that this finding had low credibility (Table III).

HRQL at one-year post-injury. One year post-injury, most patients had not regained their pre-injury HRQL by any of the three outcome measures (p < 0.001). Patients' mean SF-12 PCS at one year was 10.01 (95% confidence interval (CI) 9.38 to 10.64) points lower than their pre-injury score, and their mean SF-12 MCS was 2.61 (95% CI 1.97 to 3.25) points lower than prior to injury. Patients' EQ-5D mean utility scores were 0.15 (95% CI 0.14 to 0.16) lower than

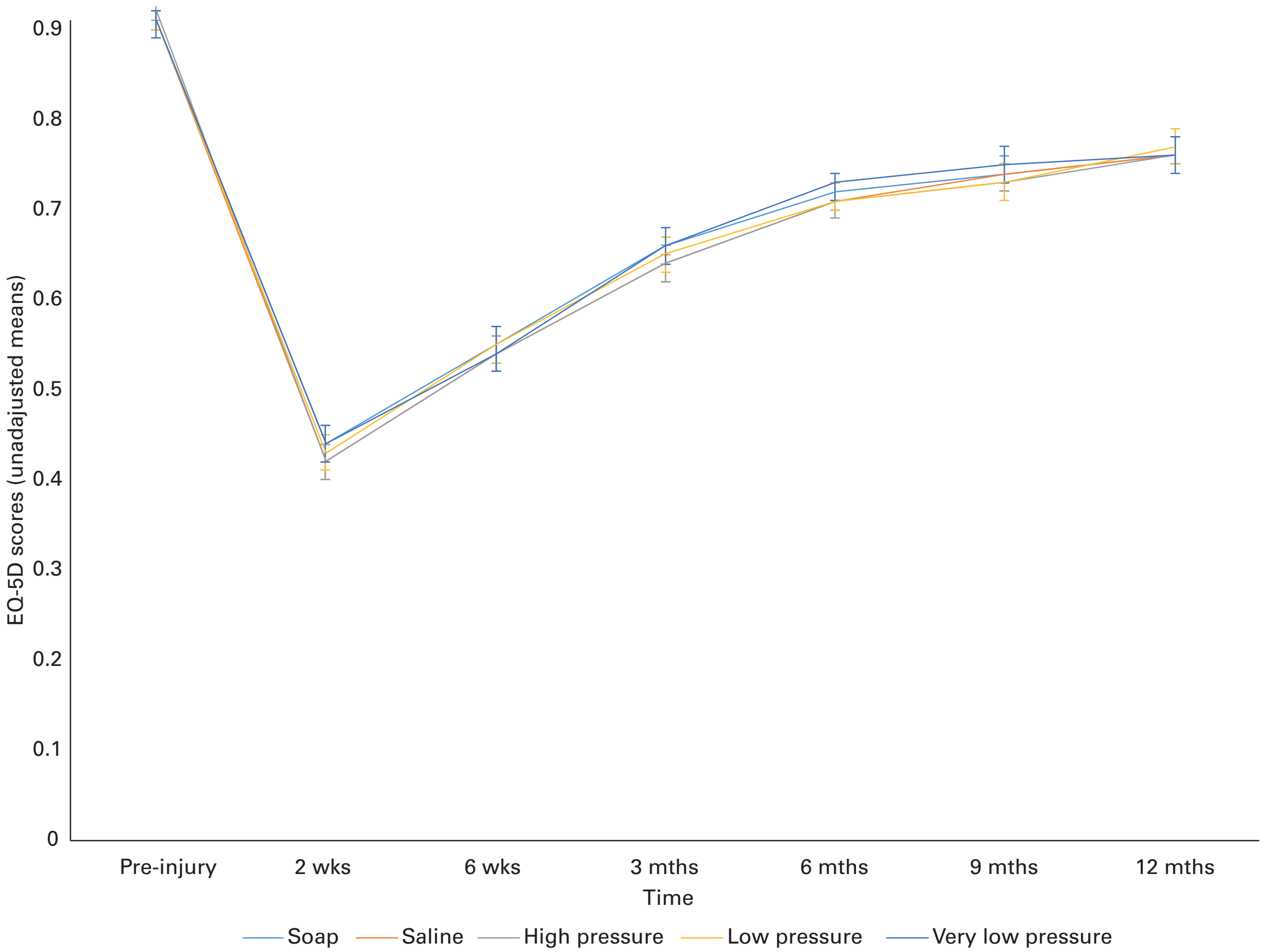

Fig. 3

EuroQol-5 Dimensions (EQ-5D) utility scores over time by solution and by pressure.

pre-injury. At one year, patients had returned to 81% of their PCS, 95% of their MCS and 84% of their ED-5D utility score.

Discussion

We found no differences between irrigation pressures in the SF-12 PCS, SF-12 MCS and EQ-5D utility score. This echoes the findings of our primary study. Analysis of the SF-12 and the EQ-5D did not capture the difference between the composition or pressure of the delivery system for the irrigation solutions which was seen in our primary study. This may have been because the outcome measures were not sufficiently responsive to capture the relatively small differences in HRQL resulting from only 41 more patients undergoing re-operation in the soap group when compared with the saline group.

In our analysis of the SF-12 PCS, the significant interaction ($p = 0.032$) between solution and pressure was unexpected, given that the initial FLOW analysis had found no such interaction. The size of the interaction was relatively small, constituting less than half of the minimum important difference of five points for the SF-12 PCS. No such interaction was seen with the SF-12 MCS, for the EQ-5D utility score, or in the re-operation rate in the original study. There is no basic scientific rationale to support the existence of such an interaction. Consequently, based on the application of the adapted criteria, we concluded that the observed interaction was not highly plausible, and was most likely a spurious finding.

We found that patients with open fractures had not returned to their pre-injury status at one-year post-injury. This is in keeping with the results of the Study to Prospectively Evaluate Reamed Intramedullary Nails in Tibial Fractures (SPRINT) trial, which also reported a reduction of 10 points in the PCS of the SF-36 over the same time period in open and closed tibial fractures.[19] The EQ-5D scores were 0.15 points lower at one year, which also represents a clinically important difference.[11] The SF-12 MCS, by contrast, was 2.66 points lower and hence not a clinically important difference. These findings are also consistent with the results of the SPRINT trial, which found the SF-36 MCS to be approximately 2 points lower at one year.[19] Similarly, a recent study of functional recovery in patients with tibial fracture reported that HRQL had not

Table II. Effect of treatment group on Short Form-12 physical component scores (PCS) at 12 months

	Mean difference between 12-month PCS (95% CI)*
At high pressure	
Soap *vs* saline	1.18 (0.02 to 2.33)
At low pressure	
Soap *vs* saline	0.45 (-0.71 to 1.61)
At very low pressure	
Soap *vs* saline	-0.99 (-2.16 to 0.18)
With soap	
High *vs* low	-0.12 (-1.28 to 1.04)
High *vs* very low	0.51 (-0.64 to 1.67)
Low *vs* very low	0.63 (-0.53 to 1.79)
With saline	
High *vs* low	-0.84 (-2.00 to 0.31)
High *vs* very low	-1.65 (-2.82 to -0.48)
Low *vs* very low	-0.81 (-1.98 to 0.36)

*from the main 3-level model
CI, confidence interval

Table III. Assessment of credibility of interaction between pressure and solution for Short Form (SF)-12 physical component scores (PCS)

Criteria*	Assessment
Is the interaction variable a characteristic measured at baseline or after randomization?	Measured at the time of randomisation
Is the effect suggested by comparisons within rather than between studies?	Yes, it is suggested by comparisons within a single study rather than between studies
Was the hypothesis specified *a priori*?	Our *a priori* hypothesis was that there would be an interaction between pressure and solution
Was the direction of the interaction effect specified *a priori*?	We were unable to find a compelling reason to specify a direction of a possible effect modification
Was the interaction effect one of a small number of hypothesized effects tested?	We looked at the following three interactions: randomized solution with randomized pressure, randomized solution with time of HRQL assessment and randomized pressure with time of HRQL assessment
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	We obtained p = 0.032 for the interaction term, which suggests a low likelihood that chance explains the apparent effect
Is the significant interaction effect independent?	The interaction was not influenced by the inclusion of other interaction terms in the analysis
Is the size of the interaction effect large?	No, the size of the effect is less than half of the minimum clinically important difference for the SF-12 PCS
Is the interaction consistent across studies?	Not applicable, as no other studies have evaluated this interaction
Is the interaction consistent across closely related outcomes within this study?	No, this interaction was not observed for the SF-12 MCS or the EQ-5D index score. Also, no interaction was observed between pressure and solution for the primary study outcome of reoperation within 12 months
Is there indirect evidence that supports the hypothesized interaction (biological rationale)	No, there is no biological rationale for the observed interaction

*Adapted from criteria developed to evaluate the credibility of subgroup analyses[17,18]
HRQL, health-related quality of life; EQ-5D, EuroQol-5 Dimensions

returned to baseline at one year or at five years post-injury.[20] Several other studies in the literature reflect this.[21-23]

A strength of our study is its large, multicentre, randomized controlled nature, with a sample size that exceeds the *a priori* calculation, and its use of standardized, validated outcome measures. This is one of the largest studies to date of its kind and the inclusion of over 40 clinical sites in five countries increases the ability to generalize from our results.

Despite these strengths, our study has several limitations. The method of recording pre-injury quality of life may be prone to recall bias, although previous research has suggested that the level of bias is minimal.[24] We did not include any anatomical- or disease-specific outcome measures; typically, these do not provide such granular data on the global effect on HRQL and add a significant documentation burden to a trial enrolling patients with potentially diverse patterns of injury. This can, in turn, affect recruitment and retention rates.

This study may also be limited by its follow-up. Although one year is a frequently used follow-up period in fracture research, it may be insufficient to evaluate recovery fully. We were able to include 76% of patients enrolled in the FLOW study in this analysis; while this demonstrates a not insignificant loss to follow-up, this is a comparable proportion with that seen in previous orthopaedic trauma trials.[19]

These results show that neither irrigation pressure nor the composition of the solution have an effect on patients' HRQL within 12 months of open fracture. Despite modern fracture implants and high-quality care, patients are not returning to pre-injury status within 12 months. This can guide both surgeon and patient expectations after open fracture. It also suggests that factors other than surgical treatment may be important, and that non-surgical interventions may be necessary to help patients recover.

Future research needs to look beyond surgical technique and consider the influence of psychological support, social circumstances and co-morbidity on outcome. Although generic measures detected decrements in HRQL at one year, they may not be sufficient to capture the much smaller differences in clinically important outcomes in open fracture trials. Future methodological research is needed to understand better the assessment of HRQL in patients with open fractures.

Take home message:

- Irrigation solution and irrigation pressure do not have an effect on 12-month post-open fracture HRQL.
- Despite the use of modern fracture implants and high-quality surgical care, patients sustaining open fractures do not return to their pre-injury HRQL at 12 months post-injury.

Supplementary material

A full list of the FLOW investigators and details of the funding is available alongside the online version of this article at www.bjj.boneandjoint.org.uk

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Author contributions:

S. Sprague: Designing the study, Analysing the data, Interpreting the results, Drafting and reviewing the manuscript; on behalf of the FLOW investigators.
B. Petrisor: Principal investigator for the FLOW pilot and definitive trials, Conception of the study, Reviewing the manuscript; on behalf of the FLOW investigators.
K. Jeray: Principal investigator for the FLOW pilot and definitive trials, Conception of the study, Reviewing the manuscript; on behalf of the FLOW investigators.
P. McKay: Designing the study, Drafting and reviewing the manuscript; on behalf of the FLOW investigators.
D. Heels-Ansdell: Designing the study, Analysing the data, Interpreting the results, Drafting and reviewing the manuscript; on behalf of the FLOW investigators.
E. Schemitsch: Providing clinical expertise regarding the design of the study, Interpreting the results, Reviewing the manuscript; on behalf of the FLOW investigators.
S. Liew: Providing clinical expertise regarding the design of the study, Interpreting the results, Reviewing the manuscript; on behalf of the FLOW investigators.
G. Guyatt: Designing the study, Analysing the data, Interpreting the results, Drafting and reviewing the manuscript; on behalf of the FLOW investigators.
S. D. Walter: Designing the study, Analysing the data, Interpreting the results, Drafting and reviewing the manuscript; on behalf of the FLOW investigators.
M. Bhandari: Principal investigator for the FLOW pilot and definitive trials, Conception of the study, Reviewing the manuscript; on behalf of the FLOW investigators.

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