Δ Are Large Clinical Trials in Orthopaedic Trauma Justified?

*Sheila Sprague, PhD[1]; Paul Tornetta III, MD[2]; **Gerard P. Slobogean, MD**[3]; Nathan O'Hara, MHA[4]; Paula McKay, BSc[1]; Diane Heels-Ansdell, MSc[1]; Brad Petrisor, MD[5]; Kyle Jeray, MD[6]; Emil H. Schemitsch, MD[7]; David Sanders, MD[8]; Mohit Bhandari, MD, FRCSC, PhD[9]; FLOW Investigators*
[1]*McMaster University, Ontario, CANADA;*
[2]*Boston Medical Center, Boston, Massachusetts, USA;*
[3]*University of Maryland, Baltimore, Maryland, USA;*
[4]*University of Maryland School of Medicine, Baltimore, Maryland, USA;*
[5]*Hamilton General Hospital, Ontario, CANADA;*
[6]*Greenville Health System University Medical Center, Greenville, South Carolina, USA;*
[7]*St. Michael's Hospital, Toronto, Ontario, CANADA;*
[8]*Victoria Hospital, Ontario, CANADA;*
[9]*MacOrtho Research, Ontario, CANADA*

Purpose: Large definitive clinical trials in orthopaedic trauma are expensive, challenging, and time-consuming to conduct. In times of limited research funding, their value is questioned as it costs several million dollars to answer one or two clinical questions and results may not be translated into practice for 5 to 8 years following initiation of the trial. The objective of this study is to evaluate the necessity of one such large clinical trial using data from the FLOW (Fluid Lavage of Open Wounds) trial.

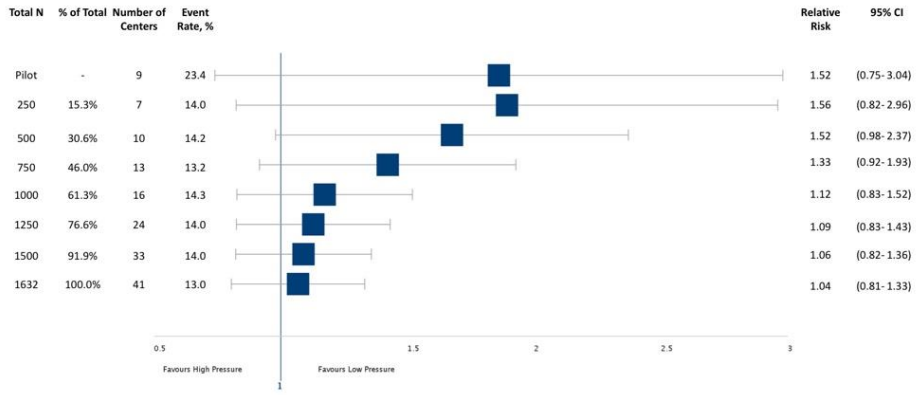
Methods: The FLOW pilot study and trial were factorial randomized controlled trials that evaluated the effect of different irrigation solutions and pressures on reoperation within 12 months for infection, wound healing, or bone healing. To evaluate the usefulness of this large trial, we analyzed the data from the pilot study and then the definitive trial in increments of 250 patients until the final sample size was reached. At each increment we calculated the relative risk (RR) and associated 95% confidence interval (CI) for the treatment effect. We then compared the results that would have been reported at the smaller enrollments with those seen in the final, adequately powered study.

Results: The pilot study analysis of 89 patients and the initial incremental enrollments in the definitive trial favored high pressure compared to low pressure (RR: 1.52 95% CI: 0.75-3.04; RR: 1.56 95% CI: 0.82-2.96 respectively), which is in contradistinction to the final enrollment, which found no difference between high and low pressure (RR: 1.03 95% CI 0.81-1.33) (Fig. 1a). In the soap versus saline comparison, the pilot study suggested that the reoperation rate was higher in the saline group (RR: 0.98 95% CI: 0.50-1.92), whereas the definitive trial found the opposite, that the reoperation rate was higher in the soap treatment arm (RR: 1.28 95% CI: 1.04-1.57) (Fig. 1b).

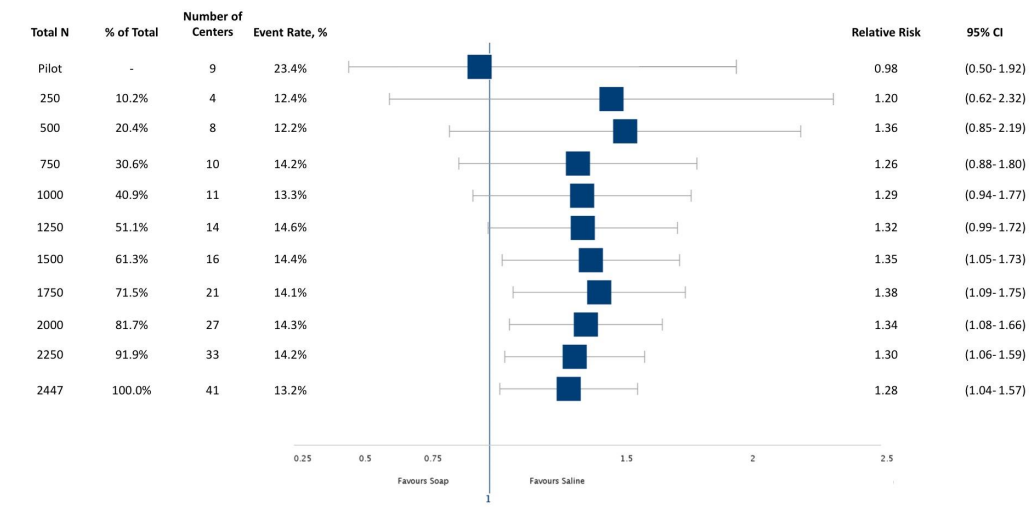
Conclusion: Our findings suggest that the FLOW pilot study and early stopping of the trial would have led to erroneous conclusions in the management of open fracture wounds. One of the major questions (irrigation pressure) changed from a substantial difference to a finding of no difference. More importantly, the results of the second major question, namely whether soap reduced the risk of event, changed from suggesting an advantage to using

Δ OTA Grant
See pages 49 - 106 for financial disclosure information.

soap to a significant finding of soap increasing the risk of reoperation. While many readers understand that trials may be underpowered, few realize that truly erroneous conclusions may come from smaller studies, including a reversal of the initial findings. These data highlight the need for large clinical trials in the field of orthopaedic trauma.



A.



B.

Figure 1: The effect of high vs. low pressure (A) and soap vs. saline (B) on patients enrolled in the [BLINDED] trial at different sample sizes

The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or medical device he or she wishes to use in clinical practice.