INternational **OR**thopaedic **MU**lticenter **S**tudy in Fracture Care (**INORMUS**)

PROTOCOL

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Principal Investigators

Mohit Bhandari MD, PhD, FRCSC
Centre for Evidence-based Orthopaedics
Division of Orthopaedic Surgery
Department of Surgery
McMaster University
293 Wellington Street North, Suite 110
Hamilton, Ontario L8L 8E7
Tel: 905-527-4322 x44490
Fax: 905-523-8781
Email: bhandam@mcmaster.ca

Philip Devereaux, MD, PhD, FRCPC
Perioperative Medicine & Surgical Research Unit
Population Health Research Institute
McMaster University
David Braley Research Building, Room C1-116
30 Birge Street
Hamilton, Ontario L8L 0A6

Methods Centre:

Division of Orthopaedic Surgery
Department of Surgery
McMaster University
293 Wellington Street North, Suite 110
Hamilton, Ontario L8L 8E7
Tel: 905-527-4322 x44981
Fax: 905-523-8781
Email: silviali@mcmaster.ca

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LIST OF ABBREVIATIONS

Abbreviations are listed in alphabetic order:

CRF	Case Report Form
EDC	Electronic Data Capture
INORMUS	INternational ORthopaedic MUlticentric Study in fracture care
LMICs	Low-Middle Income Countries

Study Summary

Title	**IN**ternational **OR**thopaedic **MU**lticenter **S**tudy in Fracture Care
Short Title	INORMUS
Methodology	Global, multi-center, observational study
Study Centre(s)	McMaster University, Hamilton, Canada (Coordinating Centre) Multiple clinical sites in Africa, Asia, and Latin America
Number of Participants	40,000
Primary Research Objectives	To determine among adult individuals admitted to hospital with musculoskeletal trauma (e.g. fractures or dislocations): 1. The incidence of major complications (mortality, re-operation and infection) as a composite outcome and as individual components within 30 days post-hospital admission. 2. The factors (system and patient variables) associated with the composite of major complications (mortality, re-operation and infection) within 30 days post-hospital admission.
Secondary Research Objective	To determine the rates of major complications within 30 days post-hospital admission by type of fracture treatment provided (e.g. splinting versus operative fixation).
Diagnosis and Main Inclusion Criteria	This study has minimal exclusion criteria by design. All patients 18 years of age or older admitted to a recruiting hospital for treatment of an orthopaedic injury that occurred within 3 months will be eligible for participation. Patients who are diagnosed with an orthopaedic fracture, dislocation, or fracture dislocation of the appendicular skeleton or spine will be included.
Study Outcomes	The primary outcome is mortality within 30 days from hospital admission for all of our research objectives. The secondary outcomes are re-operation and infection within 30 days from hospital admission.
Duration of Patient Follow-Up	Study participants will be followed until 30 days post hospital admission.

1 Introduction

This document is a protocol for a human research study. It is a multi-centre, observational cohort study designed to inform estimates of the global burden of orthopaedic injury.

Most orthopaedic trauma is caused by common injury mechanisms such as traffic crashes and falls. These injuries are a serious cause of mortality and morbidity worldwide, with trauma being the leading cause of death in the first 4 decades of life. In contrast to the declining rates of injury seen in Western countries, low-middle income countries (LMICs) are experiencing an increase in injury rates, largely due to increased motorization in these countries.[1] Furthermore, the quality of fracture care is widely variable among LMICs. Previous attempts to characterize the fracture burden in many of these countries have proven inadequate because most LMICs lack prospective registries to document the volume of injuries, the treatments chosen, and the outcomes achieved.[2-4] Of the studies that have been performed, most have been limited by insufficient sample size, scope, and generalizability. As a result, the true burden of orthopaedic injuries in many countries remains to be explored. Identification of common trends in diagnosis, management, complications, and outcomes of orthopaedic trauma is the first step toward resolving disparities in global fracture burden.

In order to better characterize the global fracture burden and to understand factors associated with mortality, this landmark multi-national observational study of 40,000 patients in Africa, Asia, and Latin America is proposed. The International Orthopaedic Multicenter Study in Fracture Care (INORMUS) seeks to determine the incidence of major complications (mortality, re-operation, and infection) following a musculoskeletal injury, and to determine factors associated with these major complications in LMICs. This large prospective observational study coincides with the World Health Organization's Global Road Traffic Safety Decade (2011-2020) and other international efforts to reduce the burden of injury on developing populations.

2 Study Objectives

2.1 Primary Objectives

The primary objectives are to determine, among adult individuals admitted to hospital with musculoskeletal trauma (e.g. fractures or dislocations):

1. The incidence of major complications (mortality, re-operation and infection) as a composite outcome and as individual components within 30 days post-hospital admission (Principal Objective 1).
2. The factors (system and patient variables) associated with the composite of major complications (mortality, re-operation and infection) within 30 days post-hospital admission (Principal Objective 2).

2.2 Secondary Objective

The secondary objective of this study is to determine the rates of major complications within 30 days post-hospital admission by type of fracture treatment provided (e.g. splinting versus operative fixation).

INORMUS will aim to firmly establish complications following musculoskeletal trauma, understand variation in risk of outcomes across centers and countries, and explore system and patient factors to explain variations in outcomes.

3 Study Design

The INORMUS study seeks to enroll 40,000 orthopaedic trauma patients from LMICs in Africa, Asia, and Latin America. **Figure 1** outlines the overall organization of the global INORMUS initiative. **Figure 2** shows the overall study processes.

3.1 Clinical Sites

We anticipate that recruitment of study participants will take place across numerous clinical sites in Africa, Asia, and Latin America. Enrolling patients from multiple centers will help guard against regional treatment biases, and increase the generalizability of our results.

3.2 Inclusion and Exclusion Criteria

This study has minimal exclusion criteria by design. All patients eighteen years of age or older admitted to a recruiting hospital for treatment of an orthopaedic injury that occurred within three months will be eligible for participation. Patients who are diagnosed with an acute fracture, dislocation, or fracture dislocation of the appendicular skeleton (upper and lower extremities, shoulder girdle, and pelvic girdle) or spine will be included. Patients, who only have fractures of the skull, face, and ribs will not be eligible. We will exclude patients who are unwilling to comply with our follow-up schedule.

3.3 Participant Enrolment

Participating centers will identify eligible patients (≥ 18 years of age) with a history of an acute injury that occurred within 3 months, through direct emergency department referral. The orthopaedic team at the hospital will conduct a history and physical examination. If the patient meets the eligibility criteria for the study, the designated study personnel will obtain informed consent and complete the study case report forms (CRFs).

3.4 Data Collection

A Research Coordinator or member of the research team at each participating clinical site will obtain data from the patient, surgeons involved in the case, and/or the medical record where available. She or he will then complete the CRF and enter this information into the electronic data capture (EDC) system. The CRFs are the primary data collection instrument for the study and all data requested on the CRF will be recorded.

3.5 Study Outcomes

The proposed research design is a multicenter, prospective observational study to identify associations between important patient outcomes and demographic, injury, treatment, and hospital factors. The primary outcome variable will be mortality within 30 days from hospital admission for all research objectives. Secondary outcome variables will include re-operation and infections within 30 days from hospital admission for the incidence, factors, and treatment objectives. Re-operations will be defined as any surgical procedure performed on the patient that was not anticipated during the initial operative or non-operative definitive management plan. Several predictor variables of interest will be considered including patient demographics, fracture

type, open injury, poly-trauma, time to treatment, and hospital characteristics. The CRF is the primary data collection instrument for the study and the designated study personnel will complete the CRFs for each research participant. They will obtain data from the patient, their surgeon and the medical record.

3.6 Patient Follow up

Study participants will be followed for 30 days post-hospital admission. If previously discharged from the hospital, patients may be seen at their one month clinic visit or contacted via telephone. We will only withdraw patients if patients withdraw consent for participation.

3.7 Patient Safety and Confidentiality

This is an observational study that will not dictate the patients' treatment. There are no anticipated risks to the safety of the study participant. All participants will have a numeric identification number and patient names and other direct identifiers will not appear on the case report forms. Data analysis will be conducted on de-identified data and only group data will be presented. The participants may benefit from the additional surveillance provided through this study which may be above standard of care.

3.8 Data Management

All participants will have a numeric study identification number; patient names and identifiers will not appear on the CRFs or be submitted to the INORMUS Methods Centre (McMaster University). Each site will maintain a master sheet with identifying information during the enrolment period to ensure that multiple entries into the database are not made for the same patient. Study personnel at each participating clinical site will ensure the paper-based CRF is complete prior to entering the data into the secure electronic data capture (EDC) system database that is maintained at the INORMUS Methods Centre (McMaster University). Obtaining a complete dataset across participating sites is critical to the success of this study. Upon receipt of the data, the personnel at the INORMUS Methods Centre will make a visual check of the data. They will query all missing data, implausible data, and inconsistencies and prepare query reports to send to each of the clinical sites. Methods Centre personnel will have frequent telephone calls with the clinical sites to discuss and resolve these queries. Once all queries have been resolved, the data will be marked clean in the EDC system.

3.9 Trial Management

Under the direction of the Principal Investigators, the INORMUS study will be coordinated through the INORMUS Methods Centre at McMaster University. A Senior Research Coordinator from the INORMUS Method Centre will be responsible for the overall day-to-day management of this project. The Methods Centre already possesses the modern clinical research infrastructure that is necessary to conduct a clinical study of this large magnitude **(Figure 1 and 2).**

We have assembled an INORMUS Global Steering Committee whose members will provide guidance and direction to the study. The committee members were selected based on their extensive experience conducting research in LMICs and/or their methodological expertise for large-scale observational studies. Specific responsibilities will include reviewing and approving key study documents and working together to resolve any challenges that arise during the study. The

Steering Committee members will communicate via telephone and email with the Principal Investigator as questions arise, as well as participate in frequent teleconferences. They will also receive frequent updates as the study progresses.

The Operations Committee, which includes the Principal Investigators and several other key members of the Steering Committee, will be responsible for the overall conduct of the INORMUS study.

Each of the five jurisdictions will be assigned one or more lead investigators who will be responsible for overseeing the study in their jurisdiction. Specific responsibilities may include clinical site selection, communicating with clinical sites, clinical site training, ensuring that the protocol is followed at the clinical sites, ensuring that participants are enrolled in a timely manner, and helping the clinical sites to maintain high quality data. The lead investigators will work closely with the Senior Research Coordinator at the Methods Centre to help to resolve any challenges that arise.

4 Statistical Methods

4.1 Sample Size

Our sample size calculation is based upon our second principal objective (i.e. to determine factors predictive of in-hospital 30-day mortality following musculoskeletal trauma (e.g. fractures, dislocations)). Of the 3 study objectives, this is the one that requires the largest number of patients to ensure the stability of the prediction model.

Our ongoing FLOW multi-centre clinical trial evaluating patients with severe open fractures (largely recruiting across North America and Australia) has a 30 day mortality of 0.67%. However, our INORMUS pilot study, focused in a LMIC, demonstrated a 30 day mortality rate of 1.7% (95% CI, 1.4-2.2%). The pilot study results are consistent with other data suggesting the substantially increased mortality from fractures across LMICs. Given the importance of avoiding an underpowered study that results in an overfitted model, we have focused our sample size estimation for the INORMUS definitive study using a 2.0% primary event rate. By achieving adequate power for our primary analysis, we will be well powered for secondary analyses given re-operation and infection rates from our pilot study both exceeded 6% (6.6%, 95% CI: 6.0-7.3% and 6.2%, 95% CI: 5.8-7.1% respectively). For our primary outcome (i.e. incidence of mortality) a sample size of 40,000 patients with an event rate of 2.0% provides a precise estimate with a 95% confidence interval of 1.9-2.2% (**Table 1**).

For our secondary outcome, a multivariable analysis will be undertaken to determine the clinical predictive model. Simulation studies demonstrate that logistic models require 12 to 15 events per predictor to produce stable estimates. Fifty-six predictors will be examined in our multivariable analysis (**Table 2**). Variable selection was informed by our pilot study and a critical review of the available evidence for predictive factors in orthopaedic trauma outcomes. Considering the anticipated 2.0% event rate, our sample size of 40,000 patients will provide a stable model.

4.2 Data Analyses

For the principal objective, the proportion of patients suffering a major complication including mortality, re-operation or infection will be determined along with associated 95% confidence intervals. To address the other principal objective and secondary objective, a multivariable logistic regression analysis will be utilized to develop a generic model in which the dependent variable is mortality at 30 days after hospital admission and the independent variables are the 21 pre-

operative patient characteristics, 14 injury characteristics, 8 hospital admissions details, and 13 orthopaedic specific injury characteristics (**Table 2**). For all logistic regression analyses, forced simultaneous entry will be utilized. The multivariable logistic regression analysis will be completed again with an independent country variable to determine if there is a country effect. Bootstrapping will be utilized to assess the internal validity of all models because this technique is superior to cross-validation and jack-knife techniques. Sensitivity analyses will be performed to account for: 1) possible clustering within a site using a generalized estimating equations model with an exchangeable correlation structure, 2) missing values using a multiple imputation analysis, assuming the data are missing at random, and 3) death as a competing risk. We will report odd ratios (OR) for logistic regression or hazard ratios (HR) for survival analysis and corresponding 95% confidence intervals and associated p values for all models. All a priori tests will be two-sided with a significant p value set at alpha = 0.05.

5 Ethical Considerations

This study will be conducted according to international standards of Good Clinical Practice, applicable government regulations, and applicable institutional research policies and procedures as relevant to observational studies.

This protocol and any amendments will be submitted to a properly constituted independent Research Ethics Board, in agreement with local legal prescriptions, for formal approval of the study conduct at each clinical site. The decision of the Research Ethics Board concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to INORMUS Methods Centre before commencement of this study.

Research personnel will approach all potentially eligible participants and they or their proxy's will sign an informed consent form to indicate their willingness to participate in the INORMUS study. Confidentiality will be maintained both at the local clinical site and the INORMUS Methods Centre through a secure, password-protected EDC system and anonymization.

6 References

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4. Bhalla K, Harrison JE, Shahraz S, Fingerhut LA. Availability and quality of cause-of-death data for estimating the global burden of injuries. *Bulletin of the World Health Organization*. 2010; 88: 831-8C.

5. Foote CJ, Petrisor B, Beyene J, Devereaux PJ, Dhillon M, Sancheti P Kotwal P, Miclau T, Bhandari M, and the INORMUS Investigators. International Orthopaedic Multicenter Fracture

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Table 1: The Number of Variables Possible to Test in a Multivariable Analysis Based Upon Various Sample Sizes, Event Rates, and the Required Number of Events per Variable

Required number of events per variable	**Primary outcome event rate**	**Number of variables possible to test in a multivariable analysis based upon various sample sizes**		
		N=35,000	N=40,000	N = 45, 000
12	1.5%	44	50	56
	2.0%	58	67	75
	2.5%	73	83	93
15	1.5%	35	40	45
	2.0%	47	53	60
	2.5%	58	67	75

Shaded cells – cells that meet or exceed the number of variables we will evaluate in our multivariable analysis

Table 2: Factors and Variables to be Included in the Regression Analyses

Factor	Variables	Number of Levels
Patient Demographics		
Location	Africa India/Nepal China Southeast Asia Latin America	4
Age	Years	1
Gender	Male/Female	1
Education/ Literacy	No Education Elementary School High School College University Professional	5
Annual household income	Rich, Upper Middle, Lower Middle, Poor	3
Current living location	Rural (Country) Urban (City)	1
Smoking history	Current smoker Non-smoker	1
Health insurance	Private Government None	2
Co-morbidities	Infectious Cardiovascular Respiratory None	3
Injury Characteristics		
Mechanism of injury	Transport Fall Struck/Lifting Intentional Other	4
Injury intent	Intentional Unintentional Self-Inflicted Undetermined Other	4
Road traffic injury	Yes/ No	1
Number of orthopaedic injuries		1

Factor	Variables	Number of Levels
Non-orthopaedic injuries	Chest Abdominal Head/Neck Burns None	4
Hospital Admission Details		
Hospital type	Private Public/Government	1
How transported to hospital	Ambulance Motor Vehicle Rickshaw or similar (non-motorized) Air Transport On foot	4
Time from injury to hospital admission	Hours	1
Pre-operative antibiotics	Yes No	1
Time from injury to first antibiotic administration	Hours	1
Orthopaedic Injuries		
Location of injury	Upper Extremity Lower Extremity Spine Pelvis	3
Fracture severity	Closed Open (Types I, II, IIIA, IIIB, IIIC)	1
Fracture dislocation?	Yes No	1
Method of definitive stabilization	Operative Non-operative	1
Time from hospital admission to definitive stabilization	Hours	1
Time from injury to irrigation and debridement	Hours	1
Type of wound irrigation solution	Saline Soap Tap water	3

Factor	Variables	Number of Levels
	Antibiotic solution	
Irrigating solution delivery	High pressure irrigation Low pressure irrigation Gravity flow/IV tubing	2
TOTAL (Factors: 27)		**56**

Figure 1: Overall Organization of the Global INORMUS Initiative

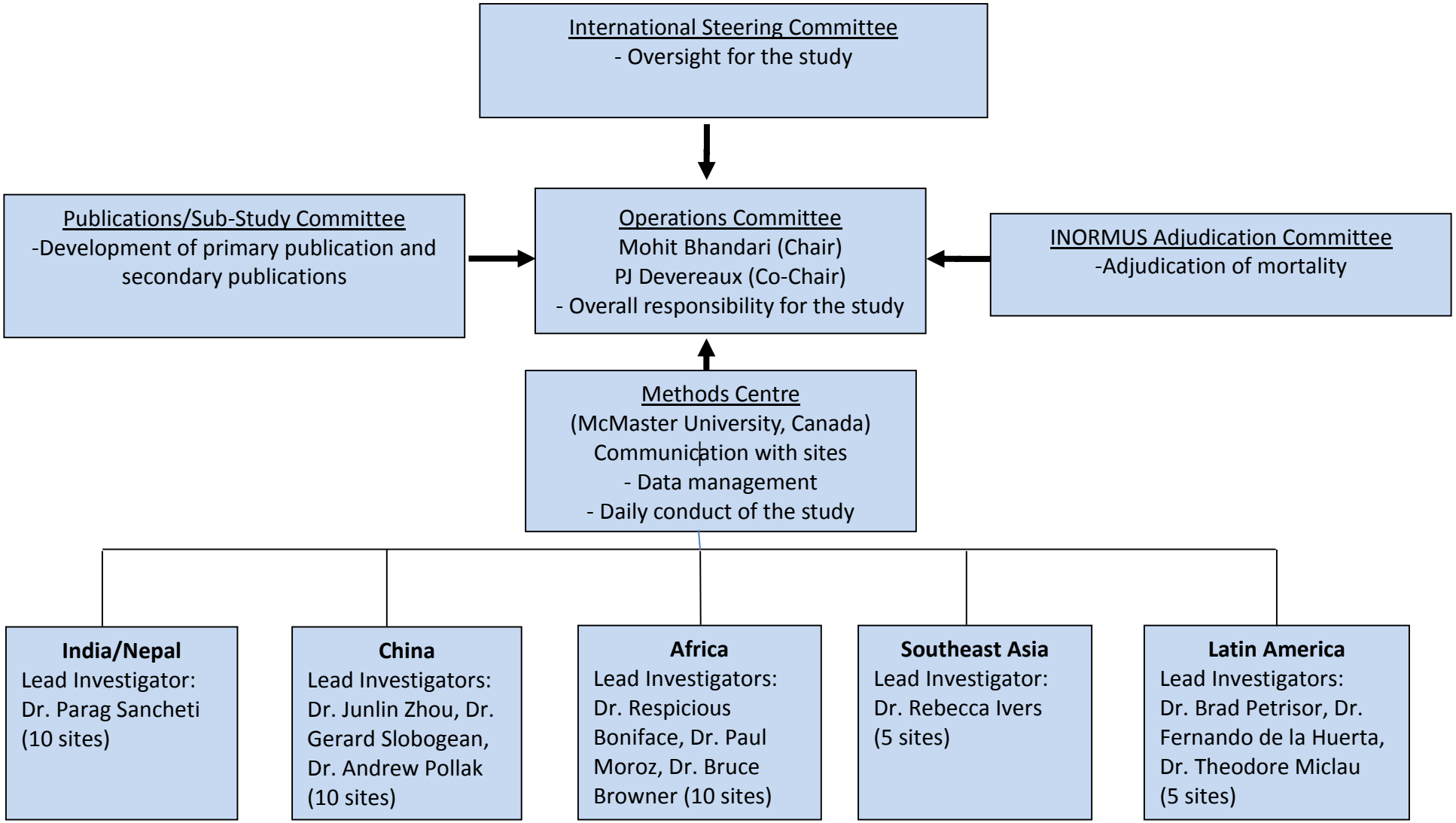

Figure 2: INORMUS Study Design