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# Rationale and design of the HIP fracture Accelerated surgical Treatment And Care track (HIP ATTACK) Trial: a protocol for an international randomised controlled trial evaluating early surgery for hip fracture patients

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# BMJ Open Rationale and design of the HIP fracture Accelerated surgical Treatment And Care track (HIP ATTACK) Trial: a protocol for an international randomised controlled trial evaluating early surgery for hip fracture patients

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## ABSTRACT

**Introduction** Annually, millions of adults suffer hip fractures. The mortality rate post a hip fracture is 7%–10% at 30 days and 10%–20% at 90 days. Observational data suggest that early surgery can improve these outcomes in hip fracture patients. We designed a clinical trial—HIP fracture Accelerated surgical Treatment And Care track (HIP ATTACK) to determine the effect of accelerated surgery compared with standard care on the 90-day risk of all-cause mortality and major perioperative complications.

**Methods and analysis** HIP ATTACK is a multicentre, international, parallel group randomised controlled trial (RCT) that will include patients ≥45 years of age and diagnosed with a hip fracture from a low-energy mechanism requiring surgery. Patients are randomised to accelerated medical assessment and surgical repair (goal within 6 h) or standard care. The co-primary outcomes are (1) all-cause mortality and (2) a composite of major perioperative complications (ie, mortality and non-fatal myocardial infarction, pulmonary embolism, pneumonia, sepsis, stroke, and life-threatening and major bleeding) at 90 days after randomisation. All patients will be followed up for a period of 1 year. We will enrol 3000 patients.

**Ethics and dissemination** All centres had ethics approval before randomising patients. Written informed consent is required for all patients before randomisation. HIP ATTACK is the first large international trial designed to examine whether accelerated surgery can improve outcomes in patients with a hip fracture. The dissemination plan includes publishing the results in a policy-influencing

## Strengths and limitations of this study

- HIP fracture Accelerated surgical Treatment And Care track (HIP ATTACK) is the first large randomised controlled trial powered to determine the effects of accelerated surgery compared with the standard of care in hip fracture patients.
- HIP ATTACK trial implemented patient engagement strategies, including research governance, trial outcome evaluation and knowledge translation.
- Patients, healthcare providers and study personnel are unblinded to patient treatment allocation; however, outcome adjudicators are blinded to treatment allocation.
- HIP ATTACK will only inform the effect of accelerated surgery versus standard care during hospital working hours and does not inform the effects outside of working hours.

journal, conference presentations, engagement of influential medical organisations, and providing public awareness through multimedia resources.

**Trial registration number** NCT02027896; Pre-results.

## INTRODUCTION

Worldwide, millions of adults suffer a hip fracture annually.<sup>1</sup> A hip fracture results in trauma, pain, bleeding and immobility. These

factors may trigger inflammation, hypercoagulability, catabolism and stress,<sup>2-5</sup> which can precipitate perioperative complications. The most commonly reported causes of short-term mortality after a hip fracture are coronary heart disease, stroke, pneumonia, sepsis and pulmonary embolism.<sup>6,7</sup> The mortality rate post a hip fracture is 7% to 10% at 30 days and 10% to 20% at 90 days.<sup>8-13</sup>

The impact of early surgery on the risk of perioperative complications and mortality in hip fracture patients was evaluated in a systematic review and meta-analysis of observational studies.<sup>14</sup> Earlier surgery was associated with a significant reduction in mortality (relative risk [RR], 0.81; 95% CI 0.68 to 0.96;  $p=0.01$ ) in five studies (4208 patients, 721 deaths). Earlier surgery was also associated with reduced risk of pressure sores (RR, 0.48; 95% CI 0.34 to 0.69;  $p<0.001$ ) and in-hospital pneumonia (RR, 0.59; 95% CI 0.37 to 0.93;  $p=0.02$ ).<sup>14</sup>

The *HIP* fracture Accelerated surgical Treatment And Care track (HIP ATTACK) Pilot Trial included 60 patients and established the feasibility of a trial of accelerated surgery in patients with a hip fracture. Among patients randomised to accelerated surgery, 30% had a major perioperative complication (ie, mortality and non-fatal preoperative myocardial infarction [MI], myocardial injury after noncardiac surgery, pulmonary embolism, pneumonia, stroke, and life-threatening and major bleeding) within 30 days of randomisation as compared with 47% of the patients allocated to standard care (HR, 0.60; 95% CI 0.26 to 1.39;  $p=0.23$ ).<sup>15</sup>

We designed the HIP ATTACK Trial to determine the effect of accelerated medical clearance and accelerated surgery compared with standard care on the 90-day risk of the following two co-primary outcomes: all-cause mortality and major perioperative complications.

## METHODS AND ANALYSIS

### Trial design

The HIP ATTACK Trial is a multicentre international, parallel group randomised controlled trial (RCT) of 3000 patients with a hip fracture that requires a surgical intervention. Patients are randomised to accelerated medical assessment and surgical repair (ie, goal of surgery within 6 hours of hip fracture diagnosis) or standard care.

### Trial population

We include patients  $\geq 45$  years of age who were diagnosed with a hip fracture during working hours, due to a low-energy mechanism, and requiring surgery. All centres are able to define their own study working hours according to the feasibility of randomising patients to the accelerated surgery within 6 hours from diagnosis. **Box 1** reports the exclusion criteria.

Currently, across Canada, 80%–90% of patients with a hip fracture undergo hip surgery within 48 hours after the diagnosis.<sup>16</sup> To minimise the variation in the timing of surgery between centres, we have only included centres

## Box 1 Exclusion criteria of the HIP ATTACK trial

Patients fulfilling any of the following criteria are excluded:

- ▶ Requiring emergent surgery or emergent interventions for another reason (eg, subdural hematoma, abdominal pathology requiring urgent laparotomy, acute limb ischemia, other fractures or trauma requiring emergent surgery, necrotising fasciitis, coronary revascularisation, pacemaker-implantation).
- ▶ Open hip fracture.
- ▶ Bilateral hip fractures.
- ▶ Peri-prosthetic fracture.
- ▶ Therapeutic anticoagulation not induced by a vitamin K antagonist, unfractionated heparin (eg, any administration of therapeutic low molecular weight heparin [ $>6000$  u/24 hours] in the 24 hours prior to enrolment) or intake of any other oral anticoagulant(s) for which there is no reversing agent available.
- ▶ Taking a therapeutic vitamin K antagonist with a history of heparin-induced thrombocytopenia.
- ▶ Refusing participation.
- ▶ Previously enrolled in the trial.

HIP ATTACK, HIP fracture Accelerated surgical Treatment And Care track.

that have  $>80\%$  of their hip fracture patients undergoing surgery within 48 hours.

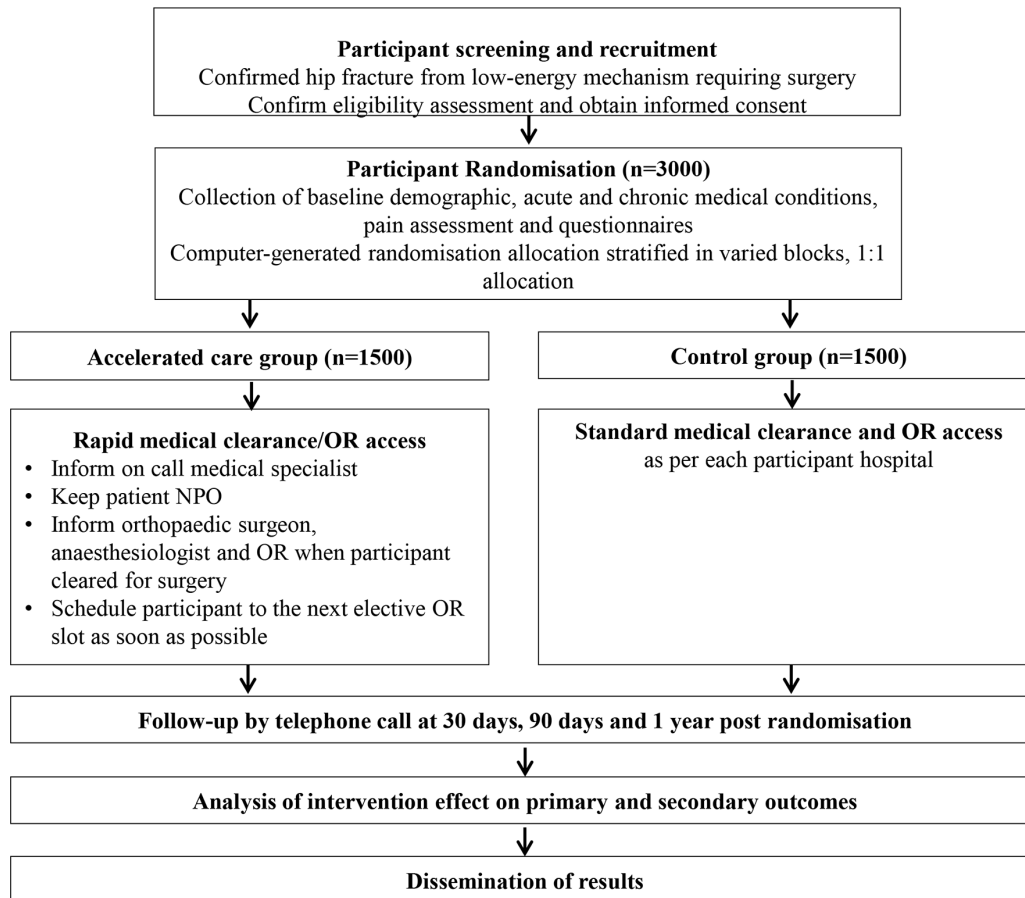
### Patient recruitment

Emergency department physicians and nurses receive a trial in-service, during which we encourage them to triage patients with a potential hip fracture for rapid assessment during working hours, similar to how patients with a potential MI or stroke are rapidly assessed. The radiology department expedites imaging of all potential hip fractures during working hours. Immediately on diagnosing a hip fracture, the emergency department physician consults the orthopaedic team on call and informs the HIP ATTACK research team about the patient. After reviewing the films and confirming a hip fracture requiring surgical intervention, the orthopaedic surgeon immediately informs the study personnel. Research personnel approach all eligible patients to participate in the trial.

### Randomisation and blinding

Randomisation occurs immediately after a patient is deemed eligible and written informed consent is obtained. Research personnel randomise the patients via an Interactive Web Randomisation System (IWRS). The IWRS is a 24 hours computerised randomisation internet system maintained by the coordinating centre at the Population Health Research Institute (PHRI), which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada.

The randomisation process uses block randomisation stratified by the centre and by the type of planned surgery (open reduction and internal fixation; or arthroplasty). We use randomly varying block sizes; the study personnel and investigators are not aware of the exact sizes. We randomise patients in a 1:1 fashion to receive accelerated



**Figure 1** The HIP ATTACK RCT flow chart. ECG, electrocardiogram; HIP ATTACK, HIP fracture Accelerated surgical TreatTment And Care track; NPO, nil per os; OR, operating room; RCT, randomised controlled trial.

medical clearance and accelerated surgery versus standard care (figure 1). The randomisation procedure ensures concealment for the purpose of minimising bias. Due to the nature of the trial, it is not possible to blind research personnel, participants or care providers involved in a patient's care. Outcome assessors are blinded to the trial intervention.

### Trial intervention

Patients randomised to accelerated care undergo medical clearance by a medical specialist (ie, internist, geriatrician, cardiologist or anaesthesiologist), who is available to quickly arrive in the emergency department for the assessment. This specialist uses his/her own individual judgement regarding management when considering any medical conditions identified, and weighs the potential benefits of delaying surgery for medical management versus the potential negative consequences of protracted exposure to the inflammatory, hypercoagulable, stress and catabolic states associated with a hip fracture. The medical specialist is aware of all the conditions that the trial consensus group believe are likely to benefit from medical optimisation before surgery (box 2).

Following medical clearance, the orthopaedic surgeon and anaesthesiologist need to agree that the patient is appropriate for surgery for the case to proceed. Patients

randomised to accelerated care (ie, medical clearance and surgery), who are therapeutically anticoagulated with a vitamin K antagonist, receive prothrombin complex concentrate to target an International Normalised Ratio (INR) <1.5.

Patients randomised to accelerated care, after obtaining medical clearance, move into the next orthopaedic trauma room or elective operating room slot depending on availability (ie, they are prioritised over scheduled elective cases). In centres with a dedicated trauma room, there is minimal impact to the workflow with case priorities being adjusted to accommodate the HIP ATTACK case booking. In addition, on evenings or weekends, HIP ATTACK patients are prioritised over other non-urgent emergency cases. Immediately after medical clearance is obtained, research personnel inform all the relevant stakeholders (ie, surgical booking clerk, orthopaedic surgeon and anaesthesiologist) to facilitate the exchange of the elective and the accelerated hip fracture case. The scheduled elective cases shift a slot forward, and therefore they occur a few hours later than originally planned.

Patients randomised to standard care undergo medical clearance based on local standard practices. After the patient is medically cleared, he/she is waitlisted for surgery according to local standard practices.

## Box 2 Conditions likely to benefit from medical optimisation prior to surgery

- ▶ Acute myocardial infarction associated with a mechanical complication or ST-elevation myocardial infarction.
- ▶ Cardiac arrest.
- ▶ Cardiogenic shock or frank pulmonary oedema.
- ▶ Respiratory failure requiring mechanical ventilation.
- ▶ Known pulmonary artery hypertension (>80 mmHg).
- ▶ Home oxygen therapy with concomitant clopidogrel.
- ▶ Presumptive bacteremia.
- ▶ Hereditary or acquired coagulopathy that cannot be corrected within 2 hours to an INR <1.5.
- ▶ Thrombocytopenia (platelets <75 ×10<sup>9</sup>/L) of unknown origin that cannot be corrected within 2 hours or in case of known chronic thrombocytopenia with Platelets <50 ×10<sup>9</sup>/L.
- ▶ Deep venous thrombosis in the last month requiring implantation of vena cava filter.
- ▶ Acute stroke within 7 days of fracture.
- ▶ Subarachnoid haemorrhage within 1 month of fracture.
- ▶ Impaired consciousness of unknown origin (GCS<12).
- ▶ Fractures during seizure without known history of epilepsy.
- ▶ Na<120 mmol/L or >155 mmol/L; or Na<125 mmol/L or >150 mmol/L with neurological symptoms.
- ▶ K>5.5 mmol/L with QRS-complex >120 ms in patients without known previous QRS-complex >120 ms or K<2.8 mmol/L not amenable to correction within 2 hours.
- ▶ pH<7.15, not amenable to correction within 2 hours.
- ▶ Indication for acute dialysis.

GCS, Glasgow Coma Scale; INR, International normalised ratio.

The central data management team monitors data quality, adherence to the trial intervention and provides a feedback to local investigators to ensure adherence to the protocol.

### Co-interventions

For patients undergoing arthroplasty, the choice of the surgical implant is left to the surgeon's discretion in both accelerated and standard care groups. All other perioperative management (monitoring, fluids, type of anaesthesia, analgesia and transfusions) and postoperative care are at the discretion of the attending anaesthesiologist, surgeon and medical specialist. Study personnel record data on co-interventions. Study investigators strongly encourage appropriate venous thromboembolism prophylaxis in all randomised patients. We also advocate early mobilisation within 12 hours of hip surgery in all randomised patients, unless medically or surgically contraindicated.

### Follow-up

All trial patients receive the same structured follow-up assessment. Research personnel follow patients throughout their time in hospital evaluating them, reviewing their medical records, ensuring trial orders are followed and noting any outcomes. The research personnel contact the patients by telephone at 30 days, 90 days and 1 year after randomisation. If patients indicate

that they have experienced an outcome, the study team obtains the appropriate documentation.

To accurately capture perioperative MI, we obtain daily troponin measurements until day 7 after randomisation. Research personnel screen all patients for postoperative delirium applying the confusion assessment method (CAM)<sup>17 18</sup> daily from day 1 to 7 after randomisation. Study personnel administer the short form quality of life (SF-36) questionnaire<sup>19</sup> to address patients' quality of life at baseline, 30 days, and 1 year after randomisation. Functional independence measure (FIM) motor domain is determined at 30 days and 1 year, as validated in hip fracture patients.<sup>20</sup> The phone administration of the SF-36 questionnaire has also been validated in hip arthroplasty patients.<sup>21</sup> Research personnel are trained in administering the CAM, FIM and SF-36. Research personnel record all the trial data on case report forms with information entered directly into an electronic data capture programme (iDataFax).

### Trial outcomes

There are two primary outcomes: (1) all-cause mortality at 90 days after randomisation and (2) composite of major perioperative complications (ie, mortality, and non-fatal MI, pulmonary embolism, pneumonia, sepsis, stroke, and life-threatening and major bleeding) at 90 days after randomisation.

Individual secondary outcomes at 90 days after randomisation include all-cause mortality, vascular mortality, non-vascular mortality, MI, myocardial injury after randomisation not meeting the third universal definition of MI),<sup>22-24</sup> cardiac revascularisation procedure (ie, percutaneous coronary intervention or coronary artery bypass grafting surgery), congestive heart failure, new clinically important atrial fibrillation, non-fatal cardiac arrest, stroke, peripheral arterial thrombosis, pulmonary embolism, deep venous thrombosis, pneumonia, sepsis, infection, life-threatening bleeding, major bleeding, acute kidney injury, new acute renal failure resulting in dialysis, peri-prosthetic fracture, prosthetic hip dislocation, implant failure, hip re-operation, time to first mobilisation, length of hospital stay, length of critical care stay, length of rehabilitation stay, new residence in a nursing home, new pressure ulcers and persistent post-surgical pain. Online supplementary appendix 1 describes all outcome definitions.

The FIM motor domain and its mobility and locomotion subscores, and the SF-36 score are assessed at 30 days after randomisation.<sup>19 25</sup> An additional secondary outcome is delirium up to 7 days after randomisation. We determine the presence of delirium using CAM, which is a validated tool for the detection of delirium in elderly hospitalised patients.<sup>17 18</sup> For the diagnosis of delirium, the CAM requires acute fluctuating changes in mental status, including inattention, incoherent thoughts and alterations in the consciousness level.<sup>17</sup>

The motor domain of FIM consists of 13 items each scored 1 to 7.<sup>26</sup> The motor domain scores range from 13

to 91, with high scores indicating higher function. The SF-36 measures health-related quality of life by scoring eight domains (physical function, role limitation due to physical health, pain, general health perception, vitality, social function, role limitations due to emotional health and mental health) from 0 to 100. High scores indicate good quality of life. The validity of the SF-36 in patients following a hip fracture is established, as well as responsiveness to changes in the SF-36 physical function domain.<sup>19 25</sup>

### Outcomes at 1 year

For long-term follow-up, the primary outcome is a composite at 1 year after randomisation of all-cause mortality and non-fatal MI, pulmonary embolism, pneumonia, sepsis and stroke. Individual secondary 1-year follow-up outcomes include all-cause mortality, vascular mortality, non-vascular mortality, MI, congestive heart failure, non-fatal cardiac arrest, coronary revascularisation, stroke, peripheral arterial thrombosis, pulmonary embolism, deep venous thrombosis, pneumonia, sepsis, new acute renal failure requiring dialysis, peri-prosthetic fracture, prosthetic hip dislocation, implant failure, hip re-operation, new residence in a nursing home, hospital readmission, persistent postsurgical pain, FIM motor domain and its mobility and locomotion subscores, and the SF-36 score.

### Adjudication of outcomes

The Event Adjudication Committee is a committee of clinicians with expertise in perioperative outcomes. These individuals are blinded to treatment allocation and adjudicate the following outcomes: myocardial injury after randomisation, MI, non-fatal cardiac arrest, stroke, pulmonary embolism, deep vein thrombosis, new congestive heart failure, pneumonia, sepsis and bleeding. All adjudicators are trained before commencing trial adjudication. We will use the decisions of the outcome adjudicators for all statistical analyses of these events.

### Statistical considerations

#### Sample size

The overall type 1 error rate for the two co-primary outcomes will be 5% (0.05) and this will be partitioned between the two co-primary outcomes, taking into account the overlap between the outcomes (ie, all-cause mortality is a subset of the composite). Assuming a 20% overlap, with the pre-specified  $\alpha$  of 0.04 for the first co-primary outcome (all-cause mortality at 90 days), the  $\alpha$  of 0.012 for the second co-primary outcome (composite) was calculated via simulation.

The sample size calculations were performed using a time-to-event analysis (Cox proportional hazards model comparison with two equal groups), two-sided  $\alpha=0.05$  using Power Analysis and Sample Size software V.13 (2014) (see table 1).

With a sample size of 3000 patients, the HIP ATTACK Trial will have 88% power to detect a relative risk

**Table 1** Sample size calculations: sample size fixed at 3000 and  $\alpha$  for the first co-primary outcome (mortality) fixed at 0.04 and the second co-primary outcome calculated at 0.012

Power calculation			
Control event rate			
Sample size fixed at 3000 and $\alpha$ for the first co-primary outcome (mortality) fixed at 0.04			
HR	12.5%	13.0%	13.5 %
0.73	0.785	0.801	0.816
0.70	0.873	0.886	0.897
0.65	0.96	0.966	0.971
Sample size fixed at 3000 and $\alpha$ for the second co-primary outcome* at 0.012 (calculated)			
HR	27.5%	30%	32.5%
0.75	0.916	0.941	0.958
0.70	0.988	0.993	0.996
0.65	0.9992	0.9997	0.9999

\*Composite outcome of major perioperative complications (ie, mortality, non-fatal myocardial infarction, pulmonary embolism, pneumonia, sepsis, stroke, and life-threatening and major bleeding).

reduction (RRR) of 30% (ie, a HR of 0.70) for the first co-primary outcome (90-day all-cause mortality) with a two-sided  $\alpha=0.04$ , assuming an event rate of 13.0% in the control group. Even with an observed RRR of 27% (ie, a HR of 0.73), the trial would have 80% power for the first co-primary outcome. The trial will also have 99% power to detect a 30% RRR (ie, a HR of 0.70) for the second co-primary outcome assuming a standard care event rate of 30% with an  $\alpha=0.012$  (two-sided). Even with an observed RRR of 25% (ie, HR of 0.75), there would be 91% power for the second co-primary outcome assuming an event rate of 27.5% in the control group.

### Main analysis

We will analyse patients in the treatment group to which they are allocated, according to the intention-to-treat principle. We will include all patients randomised in these analyses, regardless of the timing of surgery. We will compare patients allocated to accelerated medical clearance and surgery with patients allocated to standard care. We will present the binary analyses using the Kaplan-Meier estimator. We will use log-rank tests to compare the rate of occurrence of the primary outcome between the accelerated care group and the standard care group. We will use Cox proportional hazards models to estimate the effect of accelerated care on the HR for the primary and dichotomous secondary outcomes including the 1-year outcomes. We will calculate the HRs and their associated 95% CIs. We will estimate the effect of accelerated care versus standard care on SF-36 and FIM scores with a generalised linear model. We will infer statistical significance if the computed two-sided p value is  $<0.05$ .

### Subgroup analysis

Cox proportional hazards model assessing the primary outcome will provide the basis for evaluating our single planned subgroup analysis (ie, patients who present to the hospital  $\geq 4$  hours after their hip fracture). We expect a larger treatment effect in patients who present within 4 hours of their hip fracture. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at  $p < 0.05$ .

### Interim analysis

We will perform two interim efficacy analyses based on the co-primary outcomes when 50% and 75% of the patients have been followed for 90 days. The independent Trial Monitoring Committee (TMC) will employ the modified Haybittle-Peto rule of 4 SDs ( $\alpha = 0.0001$ ) for analyses in the first half of the trial (including the first planned interim analysis) and three SDs ( $\alpha = 0.00047$ ) for all analyses in the second half. For a finding to be considered significant for either co-primary outcome, these predefined boundaries will have to be exceeded in at least two consecutive analyses, three or more months apart. If either co-primary outcome fulfils these criteria, the TMC will consider initiating discussion with the Project Office Operations Committee about potentially terminating the trial.

The  $\alpha$ -level for the final analysis will remain the conventional  $\alpha = 0.05$ , given the infrequent interim analyses and associated low  $\alpha$  levels, as well as the requirement for confirmation with subsequent analyses. We will apportion the  $\alpha$  between the two co-primary outcomes in the final analysis. We will split the  $\alpha$  with the first co-primary outcome (all-cause mortality at 90 days) at 0.04 and the second co-primary outcome (composite) at 0.012, due to overlap.

At any time during the trial, if safety concerns arise, the TMC chairperson will assemble a formal meeting of the full committee. The TMC will make their recommendations to the Project Office Operations Committee after considering all the available data and any external data from relevant studies. If a recommendation for termination is being considered the TMC will invite the International Operations Committee to explore all possibilities before a decision is made.

### Trial organisation

PHRI is the coordinating centre for this trial worldwide and is primarily responsible for the organisation of the trial, development of the randomisation scheme, the study database, data consistency checks, data analysis and coordination of the study centres. The trial structure includes the following groups: the Project Office Operations Committee, International Operations Committee, Steering Committee, National Coordinators, Investigators, Coordinating Centre, and Adjudication Committee.

### Patient and public involvement

Our approach to patient engagement is guided by the Canadian Institutes of Health Research strategy for

patient-oriented research patient engagement framework spanning research governance, strategy, and methods.<sup>27</sup> Examples include (a) governance auditing—engaged patient representatives maintain an audit trail of strategy—and execution—related decisions in order to guide ongoing activities; (b) ‘Word on the Street’ videos—brief (40 to 60 s) commentaries target personal experience of our research and are shared via Twitter using Bitly software and (c) Outcome evaluation—we use an interactive audience response system so patient partners can tell us, from their perspective, which trial outcomes matter most. We use this information to inform our future trial communications strategy.

### ETHICS AND DISSEMINATION

We require documentation of Research Ethics Committee or Institutional Review Board (REC/IRB) approvals before sites are activated to enrol patients. All committees are described in detail in the Supplement File under the Supplemental Trial Groups and Investigators section. Investigators are informed of any protocol amendments, and REC/IRBs are requested to approve them. Research personnel or good clinical practice trained healthcare professionals participating in the study obtain written informed consent (online supplementary appendix 2) for each patient before randomisation. All data are stored on a centrally encrypted, high-security computer system and kept strictly confidential. The online supplementary appendix 3, presents the list of the HIP ATTACK trial participant sites and countries.

### Dissemination policy

The knowledge dissemination plan includes traditional modes of dissemination (ie, publication in a policy-driving journal, national/international conference presentations) as well as the engagement of influential medical organisations (ie, emergency medicine and orthopaedic surgery organisations). Broader dissemination will be performed by the HIP ATTACK public website (<http://www.hipattacktrial.com>), Twitter account (@HIPATTACKTrial), Facebook page and LinkedIn Profile. The Reducing Global Perioperative Risk Multimedia Resource Centre, linked to Elsevier’s entire online global readership, will disseminate slide and audioinstructional videos, full-text articles, links to abstracts and data summaries.

### DISCUSSION

Hip fractures are a worldwide health concern due to their high incidence, poor outcomes and high health economic costs. Population ageing will probably worsen this scenario in the near future. Age, male gender, clinical comorbidities, dementia, nursing home residency and surgical delay are associated with an increased risk of mortality after a hip fracture.<sup>28</sup> Surgical timing is the only potential modifiable risk factor for postoperative mortality and major complications.



Evidence from several observational studies, including systematic reviews and meta-analyses, demonstrates that early surgery is associated with better outcomes and with decreased mortality in patients suffering a hip fracture.<sup>14 29–31</sup> Uzoigwe and colleagues published prospective data on 2056 patients in UK. Patients who had surgery more than 12 hours after hip fracture diagnosis had adjusted OR of 3.8 (95% CI 1.03–14.50;  $p=0.046$ ) for in-hospital mortality compared with those who had surgery within 12 hours.<sup>32</sup>

Results from an intervention study in Canada demonstrated that coordinated, region-wide efforts directed at meeting a 48 hours benchmark for hip fracture surgery was successful in reducing time to surgery, length of stay, adjusted in-hospital and 1-year mortality.<sup>33</sup> There were 3525 preintervention and 3007 postintervention patients  $\geq 50$  years of age. Surgery within 48 hours increased from 66.8% to 84.6%, length of stay decreased from 13.5 to 9.7 median days and in-hospital mortality decreased from 9.6% to 6.8% (all  $p<0.001$ ). In-hospital mortality (HR, 0.68; 95% CI 0.57 to 0.81) and mortality at 1-year follow-up (HR, 0.87; 95% CI 0.79 to 0.96) were reduced in adjusted analyses.

Hip fracture patients who undergo surgery have worse outcomes compared with matched patients who undergo elective hip surgery.<sup>34</sup> This suggests that a hip fracture initiates processes that increase patients' risk independent of surgery. A hip fracture causes pain, immobilisation and bleeding, which trigger a cascade of inflammation, sympathetic activation, hypercoagulability and catabolism that can ultimately cause acute clinical complications (eg, thromboembolism, acute MI, infection and death). Delay in repairing a hip fracture will increase the duration of time a patient is exposed to these negative physiological stressors. It is possible that urgent surgical treatment of a hip fracture will yield benefit, similar to how rapid treatment of an acute MI and stroke have yielded benefit from rapid reversal of the underlying physiological abnormalities.

Although previous hip fracture studies provide insights into this issue, there are many examples of risk-adjusted observational studies reporting misleading results. For example, observational studies suggested harm with transfusion of older blood; however, subsequent large RCTs showed older blood was safe.<sup>35</sup> Currently, evidence on best timing to perform hip fracture surgery is based mostly on observational studies, which are at risk of residual confounding. These studies may have overestimated the effects of early surgery because sicker patients likely went to surgery later than less ill patients, due to clinical optimisation before surgery. On the other hand, observational data could underestimate the effects of ultra-early surgery, such as surgery within 6 hours, which has not been evaluated in clinical studies. Only large, high-quality RCTs can minimise bias and provide a valid estimate of treatment effects.

In HIP ATTACK, the goal in the accelerated surgery arm is to operate on patients as soon as possible, with

a target time of  $<6$  hours, which was demonstrated as feasible in the HIP ATTACK pilot.<sup>15</sup> HIP ATTACK is a large international trial powered to inform the effect of accelerated surgery on patient-important outcomes.

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