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Timing and staging of antibiotic administration and surgery for open long bone fractures of the upper and lower limbs (Protocol)

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Timing and staging of antibiotic administration and surgery for open long bone fractures of the upper and lower limbs.
Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD013555.
DOI: 10.1002/14651858.CD013555.

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[Intervention Protocol]

Timing and staging of antibiotic administration and surgery for open long bone fractures of the upper and lower limbs

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Editorial group: Cochrane Bone, Joint and Muscle Trauma Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2020.

Citation: Chan JKK, Aquilina AL, Rodrigues JN, Griffin XL, Nanchahal J. Timing and staging of antibiotic administration and surgery for open long bone fractures of the upper and lower limbs. *Cochrane Database of Systematic Reviews* 2020, Issue 3. Art. No.: CD013555. DOI: 10.1002/14651858.CD013555.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects (risks and benefits) of timing of antibiotic administration, and of timing and staging of surgical interventions, in the management of people with open long bone fractures of the upper and lower limbs.

BACKGROUND

Description of the condition

Long bones are relatively long and narrow bones, typically consisting of a shaft (diaphysis) with widenings and growth plates (epiphyses) at either end. This review considers the major long bones of the lower and upper limbs. These include the femur (thigh bone), tibia (shin bone), fibula (the other lower leg bone), humerus (upper arm bone), and the radius and ulna (the two forearm bones). The small bones of the hand, wrist, toes and forefoot are excluded from this review because they tend not to have the same clinical problems as the long bones. For open fractures of these small bones, the risks of deep infection and need for surgery are less, particularly for 'open tuft' fractures of the distal phalanges (end bones) of the fingers, which are often treated non-operatively.

Open fractures of the major long bones are complex limb-threatening injuries, in which the skin overlying the fracture site is disrupted. This predisposes the fracture to infection. Open fractures tend to be high-energy injuries, often as a result of road traffic accidents, and are associated with extensive damage to the bone and overlying soft tissues. Around 15% of people with these injuries are severely injured (defined as an Injury Severity Score of 18 or more) (Pollak 2000) and 30% to 50% may also have other injuries (Costa 2018; Court-Brown 2012).

National epidemiological data for open fracture incidence rates are scarce. The annual incidence of open long bone fractures in the UK, after excluding open fractures of the phalanges, is estimated to be 30.7 per 100,000 adults, with the tibia being the most commonly injured long bone (Court-Brown 2012). Open fractures of the finger phalanges are the most common, at 45.5%, followed by tibia and fibula fractures at 11.2%. There is a lack of data from lower-income countries (Chen 2017). However, we expect wide variations between high- and low-income countries due to socioeconomic factors and differences in health and safety regulations. Young men of working age are the most commonly affected group, although there is a growing subgroup of older people in high-income countries who sustain open fragility fractures secondary to osteoporosis and poor-quality soft tissues (Costa 2018).

Open fractures vary in their severity. The most widely used classification of open fractures is the Gustilo-Anderson classification system shown below (Gustilo 1976; Gustilo 1984).

1. Type I: open fracture with a clean wound that is less than 1 cm in length.
2. Type II: open fracture, without extensive soft tissue damage, flaps, avulsions with a wound greater than 1 cm but less than 10 cm in length.
3. Type III: an open fracture with extensive soft tissue damage; a traumatic amputation or an open segmental fracture. Can also include specific categories of open fracture such as those caused by farm injuries, fractures requiring vascular repair, or fractures that have been open for eight hours prior to treatment.
   a. IIIA: type III fracture with adequate coverage of the fracture bone, despite extensive soft tissue damage.
   b. IIIB: type III fracture with extensive soft tissue loss and periosteal stripping and bone damage (usually associated with massive contamination).
   c. IIIC: type III fracture associated with an arterial injury requiring repair.

Court-Brown 2012 reported that 44.6% of tibia and fibula fractures were type III fractures, whereas only 2.2% of open distal radius fractures were of this type.

Open fractures are emergencies, and the open nature of the injury means that the fracture is at risk of deep infection. Treatment of major long bone fractures includes antibiotics and surgery to clean the wound and debride (surgically remove) dead tissues. The fracture will usually require the fractured bone(s) to be stabilised, and reconstruction of any soft tissue defect to encourage infection-free bone repair. The most severe injuries require limb salvage, which involves major reconstructive surgery of the bone and overlying soft tissues.

For people with open fractures of the lower limb in particular, final outcome is often poor. Recovery is lengthy, with an average time to fracture union (consolidation of a fracture as a result of bone healing) for tibial fractures of 41 to 43 weeks (Gopal 2004; Keating 2000; Nanchahal 1997). Complications relating to fracture healing occur in 10% to 13% of people, and include non-union (failure of bone healing), malunion (consolidation of a fracture in a position of deformity) or delayed union (Audige 2005; Harris 2009). Despite soft tissue reconstruction, deep infection rates of up to 27% have been reported, even in specialist trauma centres (Glass 2011; Pollak 2000). Treatment for deep infection is challenging, usually comprising multiple surgeries and long courses of antibiotics. This typically continues for years after the initial injury, with the risk of antibiotic resistance in chronic wounds and even amputation in extreme cases. Following open lower limb fracture, 20% to 50% of people are permanently disabled, and 40% are unable to return to work (Seekamp 1996). Hence these injuries create enormous health, social and economic costs for both individuals and healthcare systems (Bondurant 1988; Parker 2018). There is currently limited guidance for, or published data on the outcome of, equivalent injuries affecting the upper limb.

Description of the intervention

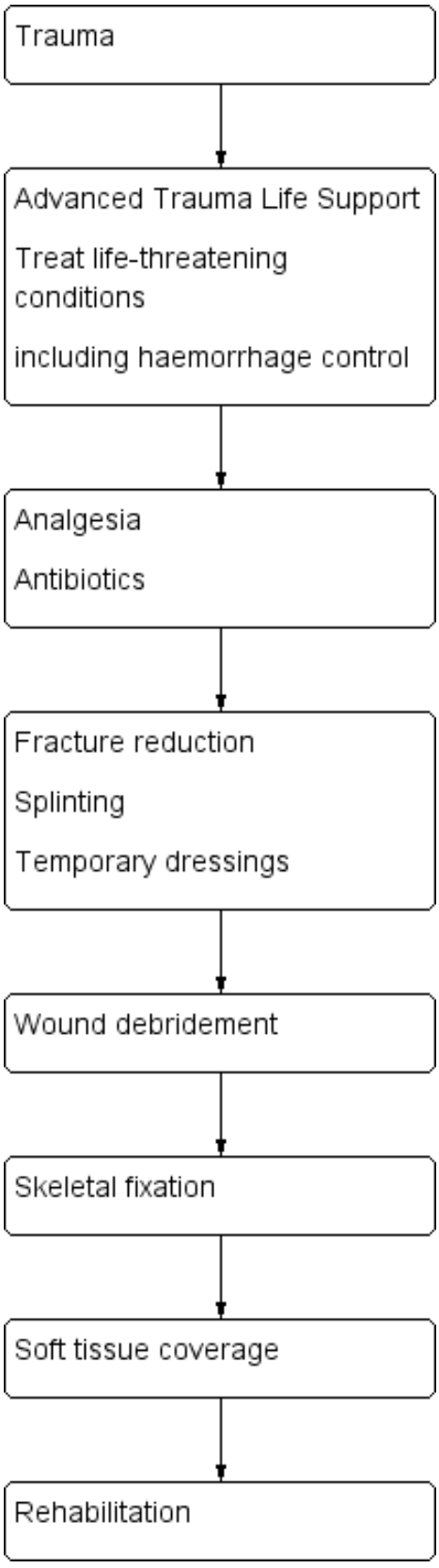
The principles of management of open fractures are to clean the wound and provide stability of the bone, as well as soft tissue cover to promote infection-free bone repair. While clinical practice varies, many countries have adopted the British Orthopaedic Association & British Association Of Plastic, Reconstructive & Aesthetic Surgeons Audit Standards for Trauma on Open Fracture (BOAST4 2017) and National Institute for Health and Care Excellence (NICE) guidance (NICE 2016).

BOAST4 2017 recommends that people with open long bone fractures are treated at a specialist centre that is able to provide combined orthopaedic and plastic surgical (orthoplastic) care. It stipulates that injuries posing the greatest threat to life, including airway problems and haemorrhage, should be treated immediately and sequentially. Once life-threatening emergencies have been stabilised, the injured limb should then be attended to.

The recommended steps are outlined in Figure 1. Following antibiotic administration, the injured limb should be examined, including an assessment and documentation of the vascular and neurological status, before realignment of the fracture and splinting. Re-examination must be completed systematically, and

with each reduction manoeuvre or splinting of the fracture. The open wound should only be handled to remove gross contaminants and, following medical photography, covered with saline soaked gauze and an occlusive dressing.

Figure 1. Flow diagram showing key stages in the management of open fractures.



Antibiotic administration

BOAST4 2017 recommends that prophylactic intravenous broad-spectrum antibiotics should be administered within an hour of injury, to reduce the risk of deep surgical site infection (SSI), as part of a standard management protocol for open fractures of long bones (BOAST4 2017). While there is a wide variation in clinical practice shown in the literature (Chang 2019), most studies report gram-positive and gram-negative coverage administered for two to three days. Most publications recommend immediate prophylactic systemic antibiotics delivered intravenously, providing gram-positive coverage, administered for up to three days for less severe injuries, but broad antimicrobial coverage for two to three days for more severe injuries.

Limb reconstruction surgery

Limb reconstruction surgery consists of three distinct steps: surgical wound debridement, skeletal fixation and soft tissue closure.

Wound debridement

Wound debridement involves the surgical removal of debris (foreign material such as road material, stones, leaves and glass) and excision of dead or irreparably damaged tissues (such as skin, muscle, bone). It is critical that a thorough debridement is undertaken, as this step is key to reducing the contaminant load and hence the risk of an infection developing in the wound. However, it remains uncertain how soon this procedure should be undertaken after the injury. It is also unclear whether any delay increases the risk of infection and, if so, by how much. According to NICE guidance, the initial surgical debridement should be performed immediately for highly-contaminated open fractures or where there is vascular compromise, within 12 hours of injury for high-energy open fractures that are not highly contaminated, or within 24 hours for all other open fractures (NICE 2016).

Reconstruction

Skeletal fixation

Skeletal fixation provides stability across the fracture site to promote bone repair. This can either be temporary or definitive, and can be in the form of an intramedullary nail, screws, plate(s) and screws, or an external fixator with pins, wires or both. External fixators (pins through the bone on either side of the fracture, connected by a bar) or plaster casts are commonly used as temporary stabilisation devices to protect soft tissues and reduce pain until definitive fixation can be achieved. Definitive skeletal fixation is the final planned orthopaedic fixation, with any further return for skeletal reconstruction categorised as an unplanned return to surgery. In cases where definitive skeletal fixation is not performed immediately following debridement under the same anaesthetic, the fracture can be temporarily stabilised and fixed definitively at a later time point. There are numerous reasons for delayed definitive fixation. These include: delayed hospital transfer, stabilisation in a multiply-injured person, and surgical preference, when the surgeons feel that it would be beneficial to perform multiple debridements in a heavily contaminated wound. There can also be logistical difficulty in arranging for joint plastic surgery input if definitive skeletal fixation and soft tissue reconstruction are planned to be undertaken in a single stage (so called 'fix-and-flap', see below).

Soft tissue coverage

Soft tissue coverage is critical to create a barrier against microorganisms causing deep infection, as well as providing the cytokine and cellular environment for bone repair (Chan 2012). At the end of wound debridement, the wound can be closed primarily, skin grafted or, if these are not possible, reconstructed using a flap. Skin grafts cannot be applied to bare cortical bone or bare tendons as they will not survive. Flap coverage is a procedure whereby the soft tissue defect is covered by bringing in vascularised soft tissues (skin and fascia or muscle, or both) from another anatomical region of the body. Depending on the location of the flap harvest site, it may or may not require detachment from its blood supply and joining to local recipient blood vessels. These are termed 'free flaps' and 'pedicled flaps', respectively.

In cases where the skin wound can be closed primarily or skin grafted, this will usually be done in the same operation as the skeletal fixation. For cases that require flap reconstruction, skeletal fixation and soft tissue reconstruction can be performed either as a single procedure, ‘fix-and-flap’, or a two-stage procedure, 'fix-then-flap', whereby skeletal fixation and soft tissue reconstruction are performed in two separate operative sessions.

How the intervention might work

The aim of antibiotic treatment and surgery is to promote infection-free fracture union, leading to a healthy functional limb. Wound debridement aims to remove all contaminants and non-viable tissues. Skeletal fixation promotes fracture union in optimal alignment, while soft tissue coverage provides a vascularised barrier between the external environment and the fracture, and hence the biological environment for the fracture to heal (Chan 2012).

Administration of antibiotics is part of the standard management protocol for open limb fractures. A previous Cochrane Review found that antibiotics are effective in reducing the incidence of wound infections compared with no antibiotics or placebo in open limb fractures (Gosselin 2004). However, the review excluded trials that compared different antibiotics, antibiotic dosages, route of administration and differences in timing or duration of administration. For fixation of closed fractures, there is also evidence that antibiotic prophylaxis significantly reduces both deep and superficial site infections (Gillespie 2010). This is likely to be pertinent to open fractures as superficial site infection can lead to wound breakdown, exposure of the fracture and risk subsequent deep infection. There is currently no international consensus on antibiotic treatment in open fractures, with regards to optimal timing of administration, route, duration and type (Chang 2019). If early antibiotic administration is found to be effective, routine prehospital treatment for people with open fractures may necessarily become the standard treatment protocol. Furthermore, evidence-based duration of antibiotic administration is important to improve antibiotic stewardship and reduce the emergence of antimicrobial resistance.

There is also uncertainty about the optimal timing of surgical intervention, and whether performing these steps (wound debridement and reconstruction) in a single stage or as separate procedures affects outcome.

BOAST4 2017 and NICE 2016 recommend wound debridement within 12 hours for wounds that are not highly contaminated and,

if necessary, flap coverage immediately at the time of debridement or within 72 hours after injury (Nanchahal 1997; NICE 2016). However, these timings are controversial and require a major trauma network (existent in England) which allows people to be brought to specialist centres that can provide this care within the recommended time frames. These time frames are currently not achievable in most countries, including other parts of the UK.

A number of studies have shown that the main microorganisms in deep infections are nosocomial (hospital-acquired) (Glass 2011; Sheehy 2010). There is evidence from retrospective cohort studies to suggest that early surgical intervention and the 'fix-and-flap' approach are associated with lower deep infection rates (Godina 1986; Gopal 2004; Liu 2012; Mathews 2015). Earlier surgical wound debridement, antibiotic treatment and soft tissue cover may reduce the deep infection rate, due to the shorter time interval during which the fracture is exposed to nosocomial microorganisms. A single-stage 'fix-and-flap' approach, compared with a two-stage technique whereby soft tissue coverage is delayed, may also reduce the risk of bacterial contamination and biofilm formation within the wound.

In some situations, particularly for people with multiple injuries, it may be necessary to perform wound debridement and delay surgical reconstruction for the affected limbs until the person is stabilised. Furthermore, in some settings, flap reconstruction may need to be delayed and performed as a separate stage, as it may be safer to perform this long and complex surgery during office hours when appropriately-skilled surgical, anaesthetic and nursing staff are available. In these situations, a temporary skeletal external fixator and temporary dressings are often used. The effect of temporary dressings, such as negative pressure wound therapy (NPWT), has been investigated. According to a recent Cochrane Review (Iheozor-Ejiofor 2018), there is no clear difference in healing rates when comparing NPWT with standard care in the treatment of open fracture wounds. The review also demonstrated uncertainty regarding whether NPWT may reduce the risk of infection, and found no clear evidence that NPWT improves pain, adverse events or the experience of receiving therapy. Furthermore, it found moderate-certainty evidence that NPWT is not a cost-effective treatment for open fracture wounds. A recent randomised controlled trial (RCT) also found that NPWT did not improve self-rated disability at 12 months, compared with standard wound dressing, among people with severe open fracture of the lower limb (Costa 2018).

Furthermore, it is critical that the wound heals satisfactorily following soft tissue coverage. Failure of wound healing may lead to chronic ulceration and deep infection. Wound healing may be compromised for many reasons, including excessive tension across the wound, infection and failure of the flap procedure, so that part or the whole of the flap dies. It remains unclear whether the timing and staging of the different surgical procedures, and in cases that require soft tissue reconstruction, the type of flap used, affect patient outcomes.

Why it is important to do this review

Despite improvements in the management of open limb fractures, there remains an unacceptably high rate of complications, particularly deep infection. Improving the management of open fractures will have a large clinical and socioeconomic impact. In England, the introduction of a multidisciplinary approach (involving orthopaedic and plastic surgeons together with microbiologists), prompt surgical intervention and a major trauma network has been associated with improved outcomes and reduced infections rates. Based on UK data, a recent RCT that compared NPWT with standard wound management in severe open fracture of the lower limb found no statistically significant difference in deep surgical site infections: 7.1% in the NPWT group and 8.1% in the standard dressing group (Costa 2018). A prospective cohort study found a 4.3% rate of further operations for early infection (Young 2019). Whilst these rates are encouraging, there remains uncertainty about whether the timings of surgical intervention and antibiotic administration affect the final outcome (Young 2019).

Evidence from randomised controlled trials on the timing and staging of surgical intervention and antibiotic administration is important to guide practice. We have not identified any previous systematic review; therefore this review is warranted. It may also provide a basis for the design of future multicentre clinical trials. Our findings may also have important implications with regards to the future design of care pathways for people with open fractures of long bones.

OBJECTIVES

To assess the effects (risks and benefits) of timing of antibiotic administration, and of timing and staging of surgical interventions, in the management of people with open long bone fractures of the upper and lower limbs.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and quasi-randomised controlled trials (where the method of allocating participants to a treatment is not strictly random, e.g. by hospital number), irrespective of publication status or language. In the unlikely scenario that there is a cluster-RCT, we will include this in our analysis. Although cross-over trials are unlikely to be feasible in this context, we will include only the first phase of such a trial if we encounter one.

Types of participants

We will include RCTs that recruit participants with open fractures of the major long bones, as described in the trial's primary report. We will exclude trials that focus on open fractures of the hand, wrist, toes and forefoot. The expected population for each comparison is likely to vary according to the question being asked. For example, not all open fracture wounds require flap coverage. Generally, cases that require flap coverage tend to be more severe injuries and may have poorer outcomes.

If there are trials that studied populations with different demographics or injury patterns, we will extract data by these subgroups where possible. We will contact authors for more information if necessary, and seek statistical advice if the design is complex.

Our main focus in this review will be on open fractures in adults, in whom the majority of these injuries occur. Although we anticipate

that the majority of trials will be of adults, we recognise that there may be studies that include data from adults and children. The biological process of bone repair differs between adults and prepubertal children (age under 12 years), as such children experience earlier bone union and much lower incidences of complications. Therefore, we do not consider that the results from prepubertal children will be generalisable to the adult population. Since the incidence of open long bone fractures is much higher in adults compared with children, we anticipate that the adult numbers will substantially outweigh those of children in mixed population trials. Where trials report data separately for subgroups, we will only extract the adults' outcomes. If the trials do not present data separately for an adult subgroup, we will include reports where the proportion of adults exceeds (or is likely to exceed) 80% of the sample.

Types of interventions

We will include studies that evaluate multidisciplinary management, including surgical intervention and antibiotic administration, for adults with open long bone fractures of the upper and lower limbs.

We plan to make the following comparisons.

1. Timing of the start of prophylactic antibiotic treatment

Early (≤ 1 hour from injury) versus late (> 1 hour from injury)

We will define early commencement of prophylactic antibiotics as the administration of one dose of any antibiotic(s) via any route (oral, enteral or parenteral), within one hour of injury, for all participants in the intervention group. Comparator groups will exclusively include participants who started taking antibiotics one hour after injury. In either group, there may be a change in choice of antibiotics or route of administration, discontinuation of antibiotics after the first dose, or discontinuation after a multi-dose course of any duration.

We will consider other definitions of 'early' used by trials that are otherwise eligible.

2. Duration of prophylactic antibiotic treatment

Terminated at soft tissue closure (any type: primary closure, skin graft or flap reconstruction) versus continued.

3. Timing of wound debridement following injury

Early (≤ 12 hours from injury) versus late (> 12 hours from injury)

In this review, we define early surgical debridement as the first surgical intervention to decontaminate the wound through the removal of debris and excision of non-viable tissues at any point within 12 hours of injury. Comparator groups will exclusively include participants whose initial surgical debridement was undertaken more than 12 hours after the time of injury. Participants may undergo immediate reconstruction, or wait varying lengths of time after debridement until reconstruction.

As above, we will consider other definitions of 'early', such as under six hours, used by trials that are otherwise eligible.

4. Reconstructive surgery: staging and timing

1. Single-stage surgery (including wound debridement, skeletal fixation plus soft tissue closure not requiring flap reconstruction) versus multi-stage surgery. In terms of the staging of surgical procedures, wound debridement, skeletal fixation and soft tissue closure can either be undertaken under the same anaesthetic or continued under another one (or more). We will consider participants who remain under general anaesthesia, but spend the period between any two surgeries in a critical care setting, to have multi-stage surgery.
2. For participants requiring definitive fixation and flap reconstruction: one-stage 'fix-and-flap' versus two-stage 'fix-then-flap'. Single-stage reconstruction is often termed ‘fix-and-flap’ (Gopal 2000); i.e. skeletal fixation, such as via an intramedullary nail, and flap cover take place under a single anaesthetic. Comparator groups will exclusively include participants who underwent two-stage reconstruction, or 'fix-then-flap', i.e. when skeletal fixation and flap cover are delivered as two separate operations.
3. For participants who undergo 'fix-then-flap' reconstruction: wound closure within 72 hours versus after 72 hours. Selection of the 72 hours threshold is based on the BOAST4 2017 and NICE 2016 recommendation that definitive soft tissue cover should be performed within 72 hours of injury, if it cannot be performed at the time of debridement. As above, we will consider other thresholds if used by trials that are otherwise eligible.

Other co-interventions and operations

We will collect details of interim or holding interventions, such as negative pressure wound therapy, but will not treat them as separate groups for comparison.

It is possible that some participants in any of the intervention groups will undergo further operative sessions; for example, to treat complications such as flap loss or wound dehiscence. We will record these as outcome measures.

Types of outcome measures

The primary focus of this review is on functional recovery and quality of life. However, we anticipate that most trials will not include patient-reported outcome measures (PROMs), but will have focused on fracture healing outcomes.

Primary outcomes

1. Limb function using validated PROMs at 6 months and 12 months; for example, the Lower Extremity Functional Scale (Binkley 1999) and Enneking Score (Enneking 1993).
2. Health-related Quality of Life (HRQoL) using PROMs at 6 months and 12 months; for example, the patient-reported EuroQol 5 Dimensional Score (EQ-5D) (Brooks 1996; Dolan 1997), Disability Rating Index (Salen 1994), Sickness Impact Profile (Bergner 1981; de Bruin 1994) and the 36-Item Short-Form Health Survey (SF-36) (Brazier 2002; Jenkinson 1999).
3. Deep surgical site infection (SSI). In preference, we will use the internationally recognised Centers for Disease Control and Prevention (CDC) definition of a deep SSI (Horan 2008), i.e. a wound infection involving the tissues below the skin that occurs within 30 days of injury. We will consider any infection that requires continuing medical intervention for 30 days after

surgery without an implant, or 90 days after surgery using an implant to be a deep infection.

Secondary outcomes

1. Delayed or non-union. There is no consensus on the definition of fracture union, and therefore on the definition of delayed or non-union. The widely accepted definition of a healed fracture in the literature is when callus is present that bridges three of four cortices on orthogonal radiographs, or an absence of pain and movement at the fracture site, or both. For the purposes of this review, we will use author definitions of non-union and delayed union. We anticipate that most studies will record time to union for each participant, but it is possible that some studies might present a proportional analysis of healed fractures at a number of fixed time points after treatment.
2. Adverse events, including:
   a. death within 12 months of injury date, from any cause;
   b. amputation following failed reconstruction within 24 months;
   c. number of participants undergoing unplanned operations within three months;
   d. number of participants undergoing unplanned operations between 3 and 12 months;
   e. flap failure – partial or total. Clinically diagnosed necrosis of part or all of the soft tissue flap that leads to exposed fracture or any internal metalwork, or necessitates further procedures (including NPWT or further surgery) to achieve soft tissue coverage;
   f. chronic pain condition: diagnosed by an appropriate clinician (e.g. lower limb surgeon, pain specialist, family doctor), i.e. not self-reported;
   g. superficial wound infection;
   h. wound dehiscence;
   i. non-primary wound related infections (chest, urinary);
   j. thromboembolic events;
   k. pressure sores.
3. resource-related outcomes:
   a. length of hospital stay for treatment of acute injury as well as all subsequent episodes related to open fracture;
   b. readmission;
   c. number of participants returning to independence by 12 months;
   d. number of participants returning to employment by 12 months.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases to find reports of relevant RCTs and quasi-RCTs:

- the Bone, Joint and Muscle Trauma Group's Specialised Register;
- Cochrane Central Register of Controlled Trials (CENTRAL) - current issue;
- MEDLINE Ovid - In-Process and Other Non-Index Citations - from 1946 onwards;
- Embase - from 1980 onwards;
- ClinicalTrials.gov;
- The WHO International Clinical Trials Registry Platform.

In MEDLINE, we will combine subject-specific terms with the sensitivity-maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011) (Appendix 1). We will use this as the basis for search strategies for the other databases listed.

We will also use the Embase RCT filter, developed by Metaxis on behalf of Cochrane (www.cochranelibrary.com/central/central-creation).

We will apply no restrictions on the basis of language or date of publication. We will translate potentially eligible foreign language studies.

Searching other resources

We will also search the following other resources:

- reference lists of short-listed articles and relevant systematic reviews to identify additional suitable studies;
- Web of Science and Scopus for cited reference searching; i.e. to identify studies that cited the included studies;
- BIOSIS, OpenGrey, National Technical Information Service (NTIS) and Grey Literature Report to identify conference abstracts and other grey literature. We will search orthopaedic-specific sources including Orthopaedic Trauma Association meetings and the Bone & Joint Journal Orthopaedic Proceedings;
- reference lists of evidence-based guidelines: Australian National Health and Medical Research Council, Canadian Medical Association Infobase, National Guideline Clearinghouse (US), National Library of Guidelines (UK), New Zealand Guidelines Group and NICE Clinical Guidelines (UK).

Data collection and analysis

Selection of studies

Two review authors (JC, AA) will independently screen all titles and abstracts to identify potential studies for review. They will compare lists of potential studies and agree on a shortlist. JC and AA will obtain copies of the full-text articles on the shortlist and review them. They will resolve any disagreements by discussion and by referral to a third review author (JN or XG). Authors will link multiple reports of the same study together. Where uncertainties remain about eligibility, we will correspond with the authors of the reports.

We will not mask titles of journals, or names of study authors and supporting institutions.

We will also present a list of excluded studies that a reader may plausibly expect to see among the included studies.

Data extraction and management

Two review authors (JC, AA) will independently use a piloted form to extract data from each trial regarding sources, study design, population, interventions and other care, and outcomes. This review aims to investigate the effects of multiple variables that may contribute to patient outcome, and hence serve as potential confounders. The data for these variables will be extracted either from the reported studies or, if not available, by contacting the

authors. We will resolve any disagreements by consensus after a third author has undertaken an additional review (JN or XG). Where necessary and practical, we will contact trialists for additional data and clarification.

Assessment of risk of bias in included studies

Two review authors (JC, AA) will independently use the 'Risk of bias' tool developed by Cochrane (Higgins 2011). We will assess seven domains, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. We will consider subjective and functional outcomes (physical function, pain, satisfaction) and objective outcomes (complications, treatment failure) separately in our assessment of blinding and completeness of outcome data. We will consider two other sources of bias: major imbalance in baseline characteristics, and other performance bias such as from imbalance in clinician training in the treatment groups. We will classify studies as 'high risk of bias', 'low risk of bias' or 'unclear risk of bias' for each domain (Appendix 2). We will resolve any disagreements by discussion and referral to a third review author (JN or XG).

Measures of treatment effect

Dichotomous data

We will calculate risk ratios (RRs) with 95% confidence intervals (CIs) for binary outcomes, such as delayed union, non-union, amputation, osteomyelitis, flap failure and death.

Continuous data

Where pooled studies report a single measure for continuous outcomes, such as duration of inpatient stay, we will report mean differences with 95% CIs. Where pooled studies within a single meta-analysis use different scales of measurement, such as for different HRQoL measures, we will use standardised mean differences (SMDs) (Hedges 1982). For continuous outcomes, we will present final scores in preference to change scores.

Unit of analysis issues

We expect that the participant will be the unit of randomisation in most of the studies. We anticipate that most participants will have one open fracture requiring treatment. Typically, measurements within individuals are correlated, and we will perform sensitivity analyses where studies include participants with more than one open fracture. Where there are multiple observations for the same outcome over time, we will use the data nearest to the upper limits of the time periods stipulated for individual outcomes, such as 6 and 12 months for HRQoL measures, in our analyses. There may be events that reoccur, or multiple treatment attempts per participant: we will ensure that we use the number of participants randomised, and not the number of treatment attempts, to calculate the effect estimate and confidence intervals. We will be alert to the unit-of-analysis issues relating to composite outcomes, such as total adverse events, where participants can have more than one individual outcome; in these instances, we will report the number of participants rather than the number of outcomes.

The interventions are not amenable to a cross-over design, but if we encounter one, we will only include data from the first phase. We do not anticipate any trials using a cluster-randomised design. However, we will seek statistical support should we find non-classical participant-level randomisation.

Dealing with missing data

We anticipate several types of missing data: unreported data, participants who withdrew or dropped out, and missing statistics. If the included trials do not report data, we will contact study authors to request assistance. Where the trials report the number of participants who provided data for any particular outcome, we will use these data. For studies which report a number of events but the denominator is unclear, we will use numbers randomised or alive at follow-up. Where feasible, we will calculate missing standard deviations from other data (standard errors, 95% CIs, exact P values). We do not plan to perform imputation for missing data. However, we will perform sensitivity analysis to assess the impact of missing data on the results.

Assessment of heterogeneity

The decision to pool the results of individual studies will depend on an assessment of clinical and methodological heterogeneity. If we consider studies sufficiently homogeneous for data pooling, we will assess statistical heterogeneity by visual inspection of the forest plots, by using the Chi^2 test with a significance level of P value less than 0.1, and the I^2 statistic. We will base our interpretation of the I^2 statistic results on those suggested by (Deeks 2019):

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity; and
- 75% to 100% may represent very substantial ('considerable') heterogeneity.

Assessment of reporting biases

In order to reduce the risk of reporting bias, we will search multiple sources to identify published and unpublished results and request unpublished data from study authors. If there are sufficient numbers of studies in a meta-analysis (at least 10), we will generate a funnel plot to assess risk of publication bias (Deeks 2019).

Data synthesis

Where appropriate, we will pool results of comparable studies using both fixed-effect and random-effects models. We will decide on the choice of the model to report by careful consideration of the extent of heterogeneity and whether it can be explained, in addition to other factors, such as the number and size of included studies. We will use 95% CIs throughout. We will consider not pooling data where there is considerable heterogeneity (I^2 statistic value greater than 75%) that could not be explained by the diversity of methodological or clinical features among trials. Where it is inappropriate to pool data, we will present trial data in the analyses or tables for illustrative purposes, and report these in the text.

Subgroup analysis and investigation of heterogeneity

We plan the following subgroup analyses, where sufficient data are available.

1. Type of soft tissue reconstruction: pedicled versus free flaps, muscle versus fasciocutaneous flaps
2. Upper versus lower limb fractures

3. Age (up to and including 60 years versus over 60 years)
4. Type of skeletal fixation: for example, intramedullary versus extramedullary devices; internal fixation versus definitive external fixation.
5. Injury severity, in terms of whether flap coverage was or was not needed
6. Time to surgical reconstruction (threshold 72 hours; NICE 2016) for comparison three (timing of debridement)).The relative importance of the timing of wound debridement and time to definitive wound closure is unclear, but we assume that early wound debridement is beneficial irrespective of the timing of surgical reconstruction; we propose to explore use this subgroup analysis to explore this assertion.

We will use the test for subgroup differences available in Review Manager 5 to determine whether there is evidence for a difference in treatment effect between subgroups (Review Manager 2014).

Sensitivity analysis

Where possible, we will assess the robustness of our findings by conducting sensitivity analyses. These will include testing the following.

1. Inclusion of quasi-randomised trials or other trials at high or unclear risk of selection bias due to inadequate concealment of allocation.
2. Inclusion of trials at high or unclear risk of attrition bias due to incomplete outcome data.
3. For missing data in individual trials:
   a. excluding trials at high risk of attrition bias;
   b. where appropriate, replacing denominators with numbers randomised for all outcomes.
4. Inclusion of trials using inadequate definitions of outcome measures, such as that for non-union.
5. Inclusion of trials and data with clear or probable unit-of-analysis issues.
6. The choice of statistical model for pooling (fixed-effect versus random-effects).

In this protocol, we have specified a number of thresholds for timing. These thresholds may vary between countries, and have varied over time within countries. We wish to explore the impact of changing these thresholds on the findings of any meta-analyses. We plan to assess the impact of our specified thresholds in the following areas.

1. Timing of antibiotic administration (comparison two). We will explore how varying the one-hour threshold alters the findings. We hypothesise that early antibiotic administration is beneficial irrespective of the timing of surgery. To test this, we will also perform a sensitivity analysis to assess how sensitive the results are to a change in this assumption. Firstly, we will include all eligible studies. Secondly, we will include only participants who met the NICE criteria with regards to the timings of wound debridement (within 12 to 24 hours, depending on injury characteristics) and wound closure or soft tissue reconstruction (within 72 hours) (NICE 2016).
2. Timing of wound debridement (comparison three). Currently, NICE guidance (NICE 2016) and BOAST4 2017 recommend surgical debridement within 12 hours of injury for high-energy open fractures that are not highly contaminated. Previously, the standards recommended a 24-hour window. We therefore plan to investigate whether the evidence supports either of these recommendations. Furthermore, many clinicians have previously used six hours as a standard. We will therefore adopt an exploratory approach to this analysis, depending on the data available, and remain mindful of these prespecified thresholds.

Assessing the quality of the evidence and 'Summary of findings' tables

We will use the GRADE approach to assess the quality of evidence for all clinical outcomes (Schünemann 2011). The quality rating ‘high’ is reserved for a body of evidence based on randomised controlled trials. We may downgrade the quality rating to 'moderate', 'low', or 'very low' depending on the presence and extent of five factors: study limitations, inconsistency of effect, imprecision, indirectness, and publication bias. We will prepare a 'Summary of findings' table for each of the main comparisons for the following outcomes:

- limb function, using recognised PROMs at 12 months;
- health-related quality of life, using PROMs at 12 months;
- deep SSI within 90 days;
- delayed or non-union;
- unplanned operations at 12 months;
- counts of adverse events, as described in Types of outcome measures;
- return to work by 12 months.

As described in Types of outcome measures, we recognise that the selection of many of the time thresholds and cut-offs are arbitrary. We will reflect any changes to these definitions in our 'Summary of findings' tables and describe the differences to the protocol where relevant.

ACKNOWLEDGEMENTS

We are grateful to Helen Handoll for her invaluable comments and guidance throughout the process of writing this protocol, and to Joanne Elliott for editorial support on the protocol. We also thank Maria Clarke for her help with the search, and Neal Thurley, who provided initial advice and suggestions regarding search strategy. We thank Lisa Cannada and David Johnson for their helpful feedback at external review of the protocol.

This protocol was supported by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to the Cochrane Bone, Joint and Muscle Trauma Group. JR is an NIHR Postdoctoral Fellow. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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APPENDICES

Appendix 1. MEDLINE search strategy

1 exp lower extremity/ or exp upper extremity/ or exp "bones of lower extremity"/ or exp "bones of upper extremity"/
2 exp Arm Bones/
3 Leg bones/ or exp Femur/ or Fibula/ or Tibia/
4 (femur or femoral or tibia* or fibula* or humor* or radius or radii or radial or ulna*).tw.
5 (leg* or foot or feet or hip* or knee* or ankle).tw.
6 (arm* or hand* or elbow* or shoulder*).tw.
7 (lower extremit* or lower limb or upper extremit* or upper limb or forelimb* or forearm*).tw.
8 Radius fractures/ or Humeral fractures/
9 Femoral fractures/ or Tibial fractures/ or exp Ulna fractures/
10 Ankle fractures/ or Shoulder fractures/
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 Fractures, Open/
13 (plateau ankle or Weber or Monteggia or Galeazzi or Hoffa or Pilon or Schatzker).tw
14 ((open or compound or trauma* or Gustilo or Tscherne or high energy) adj3 fracture).tw.
15 12 or 13 or 14
16 11 and 15
17 Debridement/
18 exp Wound Infection/pc
19 surgical wound dehiscence/ or surgical wound infection/
20 debrid*.tw.
21 Surgery, Plastic/
22 Reconstructive Surgical Procedures/
23 exp Fracture Fixation/ or exp Orthopedic Fixation Devices/
24 exp Surgical Flaps/
25 (wound* or cover* or flap* or reconstruct* or closure).tw.
26 exp Anti-Bacterial Agents/
27 (antibiotic* or antimicrob* or anti bacteria* or antibacteria*).tw.
28 (coamoxiclav or amoxicillin or cephalosporin or gentamicin or teicoplanin or cefuroxime or cefazolin or ceftriazone or penicillin or clindaymycin or aminoglycosides or vancomycin or levofloxacin or metronidazole or tazocin or piperacillin or tazobactam or linezolid or flucloxacillin or ampicillin).tw.
29 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 Randomized Controlled Trial.pt.
31 Controlled Clinical Trial.pt.
32 randomized.ab.
33 placebo.ab.
34 drug therapy.fs.
35 randomly.ab.
36 trial.ab.
37 groups.ab.
38 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39 exp Animals/ not Humans.sh.
40 38 not 39
41 16 and 29 and 40

Appendix 2. Assessment of risk of bias tool

Domain	Consider whether there was a risk of:	Author's risk of bias judgement (Low/ Unclear/ High)	Support for judgement (Quote / Comment)	Notes
Random sequence generation **(selection bias)**	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.			Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment (selection bias)	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.			Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. In particular this might apply where blocked randomisation is used in that the balancing of assignment within blocks could result in some prediction of sequence.
Blinding of participants and personnel (performance bias) ***Subjective outcomes:* e.g. Limb function and HRQoL using PROMs, physical function, pain**	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.			Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
Blinding of participants and personnel (performance bias) ***Objective outcomes:* e.g. deep SSI, amputation, unplanned operations, flap failure, wound infection, wound dehiscence, primary wound related infections, thromboembolic events, pressure sores**	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.			As above
Blinding of outcome assessment (detection bias) ***Subjective outcomes:* e.g. Limb function and HRQoL using PROMs, physical function, pain**	Detection bias due to knowledge of the allocated interventions by outcome assessors.			Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
Blinding of outcome assessment (detection bias)	Detection bias due to knowledge of the allo-			As above

(Continued)

Objective outcomes: **e.g. deep SSI, amputation, unplanned operations, flap failure, wound infection, wound dehiscence, primary wound related infections, thromboembolic events, pressure sores**	cated interventions by outcome assessors.	
Incomplete outcome data (attrition bias) ***Subjective outcomes:*** **e.g. Limb function and HRQoL using PROMs, physical function, pain**	Attrition bias due to amount, nature or handling of incomplete outcome data.	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
Incomplete outcome data (attrition bias) ***Objective outcomes:*** **e.g. deep SSI, amputation, unplanned operations, flap failure, wound infection, wound dehiscence, primary wound related infections, thromboembolic events, pressure sores**	Attrition bias due to amount, nature or handling of incomplete outcome data.	As above
Selective reporting (reporting bias)	Reporting bias due to selective outcome reporting.	We will record if the study was prospectively registered with a trial registry and whether there was a prospectively published protocol. Where a trial registry entry or protocol was available prospectively we will compare the planned outcome reporting with the final trial report.
Other bias (bias from major imbalance in baseline characteristics) **Imbalance in confounders at entry: major differences in baseline characteristics (the principal confounders considered include age, gender, type of fracture, type of prior treatment)**	Bias due to major imbalance in key baseline characteristics.	Only note or consider major and inexplicable baseline imbalance that is sufficient to lead to important confounding such as exaggeration of effect estimates.
Other bias (other performance bias) **Performance bias: for instance, provision of other interventions that should be comparable in both groups; or clear differences in personal characteristics of lead clinicians.**	Bias due to the provision of other interventions that should be comparable in both groups; or clear differences in personal characteristics of lead clinicians.	This is incompletely covered in the 'blinding (performance bias)'. Describe the measures taken to avoid performance bias, such as comparable training in the interventions.

Footnotes

HRQoL: Health-related quality of life
PROM: Patient-reported outcome measure
SSI: Surgical site infection

WHAT'S NEW

Date	Event	Description
16 March 2020	Amended	Amended affiliation details for James K-K Chan

CONTRIBUTIONS OF AUTHORS

JC wrote the protocol.
AA edited the protocol.
JR edited the protocol.
XG edited the protocol.
JN edited the protocol.

XG and JN are the guarantors of the protocol and forthcoming review.

Contributions of editorial base
Helen Handoll (Co-ordinating Editor): edited the review; advised on methodology and protocol content; and approved the final version for publication.
Joanne Elliott (Managing Editor): coordinated the editorial process; advised on content; and edited the protocol.
Maria Clarke (Information Specialist): advised on the search methods section and developed the search strategy.

DECLARATIONS OF INTEREST

JC: Cochrane UK Fellow 2017-2018.
AA: none
JR: funded by the NIHR. This represents independent research funded by the NIHR. The views expressed are the author's own, and are not necessarily those of the NIHR, NHS or the Department of Health.
XG: works within a research group which has been funded for several trials of negative pressure dressings and has published trials which may be relevant to this review. XG is fully funded by NIHR. The views expressed are the author's own, and are not necessarily those of the NIHR, NHS or the Department of Health.
JN: co-applicant on an NIHR-funded trial for negative pressure wound therapy for closed incisions in people with major trauma of the lower limb - Wound Healing in Surgery for Trauma (WHIST). He has also lectured on courses on the management of open fractures, sponsored by orthopaedic implant manufacturers.

SOURCES OF SUPPORT

Internal sources

- National Institute for Health Research, UK.

  Clinician Scientist Award funds XG full time over a five-year fellowship
- Oxford National Institute for Health Research Biomedical Research Centre, UK.

  The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC)

External sources

- No sources of support supplied