1. **TITLE OF PROJECT**
Does the use of NSAIDs amongst patients with long-bone fractures increase the risk of non-union: A structured review protocol for a systematic review.

2. **TEAM and LEAD**
Alder Hey Orthopaedic Research & Liverpool Reviews and Implementation Group (LRiG),
University of Liverpool

**Correspondence to:**
Dr Hannah Lonsdale
Consultant Anaesthetist
Sheffield Children’s Hospital
Western Bank
Sheffield
S10 2TH
hjlonsdale@gmail.com
3. **PLAIN ENGLISH SUMMARY**

Long bone fractures are breaks in the major bones in the body (forearm bones, arm, thigh and leg). These are usually caused by significant trauma, and often require surgery. They are invariably very painful. Non-steroidal drugs (i.e. Ibuprofen) are a common group of painkillers used in fracture patients. These drugs are useful because they reduce the reliance of individuals on other drugs (i.e. Morphine), which may have notable side effects, such as confusion, breathing problems, constipation. However, non-steroidal drugs may inhibit bone healing, and there is therefore a suggestion that failure of bone healing is more common when using these drugs. There is therefore on-going debate amongst orthopaedic surgeons, who fix the bone, and anaesthetists, who oversee the pain control, as to whether these drugs should be used to control pain in the perioperative period.
4. DECISION PROBLEM

1. Clarification of research question and scope

Amongst orthopaedic trauma patients does the use of non-steroidal anti-inflammatory drugs (NSAIDS) compared to treatment with alternative analgesics, increase the risk of non-union to fractures of the shaft of long bones?

2. Background

The use of non-steroidal anti-inflammatory drugs is the source of frequent contention between orthopaedic surgeons and anaesthetists amongst patients undergoing fracture surgery. Anaesthetists highlight the analgesic effectiveness of NSAIDS in musculoskeletal trauma advocating their use, whilst orthopaedic surgeons argue a theoretical delay in bone healing and a potential association with fracture non-union.

NSAIDs suppress prostaglandin production, known to be important in fracture healing. Studies in animal models demonstrate a trend towards delayed fracture healing when NSAIDs are used concurrently. However there is no robust evidence of increased prevalence of delayed or non-union of fractures in humans who use NSAIDs. Understanding the true relationship between NSAIDS and non-unions is therefore important to optimise a patient’s perioperative experience & avoid unnecessarily increasing the risk of fracture non-unions.

Summary of existing literature:
It has been demonstrated that NSAIDs are at least as effective as opioids in relief of fracture pain. A major benefit of NSAIDS is that they provide an opioid sparing effect, thereby reducing the impact of the significant side effect profile of opioids. However, non-unions of fractures are a considerable cost to an individual, and a cost to public health with almost 1,000 non-unions treated each year in Scotland alone, at a cost to the health service of up to £79,000 per case (Mills, BMJ Open, 2012).

Current randomised controlled trials are small and underpowered. Observational studies have suggested an association between NSAIDs and fracture complications including non-union, however confounders are a frequent concern that are difficult to account for in observational studies. For example, NSAIDS may be added in patients in whom pain control is challenging, which may be an independent risk factor for nonunion; this may be supported by the Bhattacharyya study (below) whereby the use of opioids was similarly identified to be a risk factor for nonunion. Case-control studies that have been undertaken to address this question are particularly complicated by recall bias.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Patient group</th>
<th>Intervention</th>
<th>t'outcome</th>
<th>Results of t'outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolphson et al. 1993.</td>
<td>RCT</td>
<td>Post menopausal women, 1st Colles' fracture (n=42)</td>
<td>Piroxicam vs. placebo for 8 weeks.</td>
<td>Bone mineral content at 8 weeks.</td>
<td>No statistical difference in primary outcome, or healing.</td>
</tr>
<tr>
<td>Giannoudis et al. 2000.</td>
<td>Case control study</td>
<td>Femoral shaft fractures in a single institution.</td>
<td>Exposure to a number of factors (inc. NSAIDs).</td>
<td>Cases (n=32): Non-union. Controls (n=67): Union.</td>
<td>NSAID use in cases - 62.5%. NSAID use in controls - 13.4%. (p&lt;0.0001)</td>
</tr>
</tbody>
</table>
Aim:
To perform a structured review of the current evidence base to assess if it is possible to quantify the risk of non-union after the perioperative use of non-steroidal anti-inflammatories, from current evidence.

Table 41 Decision problem

<table>
<thead>
<tr>
<th>Interventions</th>
<th>The use of NSAIDS within 1 month following a long bone fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients with a fracture of the diaphysis of a long bone (Humerus, radius, ulna, femur, tibia, fibula)</td>
</tr>
<tr>
<td>Comparators</td>
<td>No use of NSAIDS within 1 month following a long bone fracture</td>
</tr>
<tr>
<td>Outcomes</td>
<td>The outcome measures to be considered include:</td>
</tr>
<tr>
<td></td>
<td>• Non-union</td>
</tr>
<tr>
<td></td>
<td>• Delayed Union (&gt; 4 months to union)</td>
</tr>
<tr>
<td></td>
<td>• Reoperation</td>
</tr>
<tr>
<td></td>
<td>• Pain scores</td>
</tr>
</tbody>
</table>

5. REPORT METHODS FOR SYNTHESISING CLINICAL EVIDENCE
1. **Search strategy**

Searches will be performed in association with a medical librarian, with combinations of search terms from the following groups.

Searches will be conducted using the following Databases: Ovid SP – Medline, Cochrane database, PubMed.

The search strategy to be used will include the following components:

**Population:** Long Bone, Fractures, Human, Tibia, Femur, Fibula, Radius, Ulna, Humerus, Tibial, Femoral, Radial, Humeral.

**Interventions:** NSAIDS, Non-steroidal anti-inflammatory drugs, Anti-inflammatories, COX-2, Cyclo-oxygenase, cyclooxygenase, cyclo oxygenase, Ibuprofen, Diclofenac, Ketorolac, Naproxen, Indometacin, Dexibuprofen, Fenoprofen, Flurbiprofen, Ketoprofen, Dextroprofen, Tiaprofenic acid, Aceclofenac, Etodolac, Mefenamic acid, Meloxicam, Nabumetone, Phenybutazone, Piroxicam, Sulindac, Tenoxicam, Tolfenamic acid, Parecoxib, Celecoxib, Etoricoxib.

**Outcomes:** Non-union, Delayed union, union, Healing, healed, Re-operation, reoperation, re operation, Re-do, Complication.

---

2. **Study selection and inclusion**

Titles of articles will be reviewed and included or excluded by using covidence,

Two reviewers (Peter Skellorn & Hannah Lonsdale) will independently screen all titles and abstracts of papers identified in the initial search. Full text manuscripts of any titles/abstracts that may be eligible for inclusion will be obtained and the relevance of each study assessed according to the inclusion criteria in Table X. Titles include by one but excluded by the other reviewer will be reviewed by third independent reviewer (James Widnall).

**Table Inclusion criteria**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Randomised controlled trials and observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Patients with a fracture of the diaphysis of a long bone (Humerus, radius, ulna, femur, tibia, fibula)</td>
</tr>
<tr>
<td>Interventions</td>
<td>The use of NSAIDS within 1 month following a long bone fracture</td>
</tr>
<tr>
<td>Comparators</td>
<td>No use of NSAIDS within 1 month following a long bone fracture</td>
</tr>
<tr>
<td>Outcomes</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td></td>
<td>Non-union</td>
</tr>
<tr>
<td></td>
<td>Delayed Union</td>
</tr>
<tr>
<td></td>
<td>Reoperation</td>
</tr>
<tr>
<td></td>
<td>Pain Scores</td>
</tr>
</tbody>
</table>
This process will be documented as a flow diagram, which will make up most of the methods section of the write-up.

2. **Search Quality Assessment**

Searches will be quality assured by checking that all 5 studies in the initial summary of the current literature are present.

3. **Data extraction strategy**

Data relating to both study design and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and if necessary a third reviewer will be consulted. If time allows, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study. An example of a draft extraction form is presented in Appendix 2.

4. **Quality assessment strategy**

The quality of the individual clinical-effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted. The quality of the clinical-effectiveness studies will be assessed according to criteria based on Centre for Review and Dissemination’s Guidance for undertaking reviews in healthcare.

5. **Methods of analysis/synthesis**

The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Where sufficient data are available, treatment effects will be presented as relative risks for dichotomous data, mean differences for continuous data or as hazard ratios where appropriate along with 95% confidence intervals. Data will be presented as forest plots but only pooled when this is statistically and clinically meaningful. Studies will be grouped according to the comparator used. Heterogeneity between the included studies will be assessed by considering differences in (a) the study population, (b) intervention, (c) outcome measures, and (d) study quality. In addition, where pooling seems appropriate, forest plots will be visually assessed for the presence of heterogeneity, the Chi-squared test will be performed (p<0.1) and the $I^2$ statistic will be calculated to quantify inconsistency. Where direct comparisons are not possible, if the data allow, indirect comparisons analyses will be conducted.
6. EXPERTISE IN THIS TEAM AND COMPETING INTERESTS

This team will be made up of the following individuals, which includes clinical experts. The experts will provide insight into a range of issues related to clinical practice, potential patient characteristics that may influence clinical heterogeneity, relevant patient subgroups, model parameter estimates in the absence of economic evidence, as well as additional sources of relevant evidence such as observational studies and patient registries.

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Team lead, NIHR Clinician Scientist</td>
<td>Mr Daniel Perry</td>
</tr>
<tr>
<td>Primary Investigator (Anaesthetic Trainee)</td>
<td>Dr Hannah Lonsdale</td>
</tr>
<tr>
<td>Clinical systematic reviewer</td>
<td>Dr Janette Greenhalgh</td>
</tr>
<tr>
<td>Clinical systematic reviewer</td>
<td>Dr Irene Kreis</td>
</tr>
<tr>
<td>Orthopaedic Trainee</td>
<td>Mr Peter Skellorn</td>
</tr>
<tr>
<td>Orthopaedic Trainee</td>
<td>Mr James Widnall</td>
</tr>
<tr>
<td>Anaesthetic Consultant</td>
<td>Dr Emily Lear</td>
</tr>
<tr>
<td>Medical Librarian</td>
<td>Mr Ken Linkman</td>
</tr>
</tbody>
</table>

None of the review team has any competing interests. Any competing interests relating to any external reviewers will be declared in the final report. All correspondence should be sent to the team lead and

7. PROJECT TIMELINES

Searches to be completed by the end of September 2016, Covidence of results to identify full-text articles to be completed by end of October 2016, analysis of full-text results and writing of “results” section of paper to be completed by end of December 2016. Full write-up and submission for publication to be completed by end of March 2017.

Introduction to be written by James Widnall, redraft / edit by Hannah Lonsdale.
Methods to be written by Hannah Lonsdale, redraft / edit by James Widnall.
Conclusions to be written by Emily Lear, redraft / edit by Peter Skellorn.
Discussion to be written by Peter Skellorn, redraft / edit by Emily Lear.
Redraft /edit of whole text by Dan Perry & Helen Neary.
Clinical effectiveness data will be extracted and entered under the following headings:

**Study details**
- Author (i.e. Jones et al.)
- Year (i.e. year of publication or date of interim data collection)
- Endnote reference (endnote reference number)
- Study design (summary of study design and details of subgroup analyses [if any])
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Follow-up duration

**Intervention details**
Data for each intervention will be entered in the following format:
- Intervention (i.e. drug name[s])
- Dose(s) of intervention(s) (dose)

**Participant characteristics**
Data for each intervention will be entered in the following format:
- Number of participants enrolled (summary or ‘not stated’)
- Number of participants lost to follow up (summary or ‘not stated’)
- Average age (mean/median, range, standard deviation) (age)
- Bone involved in the fracture
- Type of fracture treatment (i.e. operative, non-operative)

**Outcomes: Definitions and measures**
- Primary outcome (Non-union, defined as a delay to union > 6 months)
- Secondary outcome (Delayed union, defined as a delay to union >3 months, reoperation, pain scores)
- Adverse effects of treatment (description of outcome as reported)

**Outcomes: Results**
Data for all outcomes specified in the protocol will be entered in the following format:
- Outcome (description of outcome measure)
- Results for intervention (summary or ‘not stated’)

---

**APPENDIX - Draft data extraction forms**

APPENDIX - Draft data extraction forms

Clinical effectiveness data will be extracted and entered under the following headings:

**Study details**
- Author (i.e. Jones et al.)
- Year (i.e. year of publication or date of interim data collection)
- Endnote reference (endnote reference number)
- Study design (summary of study design and details of subgroup analyses [if any])
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Follow-up duration

**Intervention details**
Data for each intervention will be entered in the following format:
- Intervention (i.e. drug name[s])
- Dose(s) of intervention(s) (dose)

**Participant characteristics**
Data for each intervention will be entered in the following format:
- Number of participants enrolled (summary or ‘not stated’)
- Number of participants lost to follow up (summary or ‘not stated’)
- Average age (mean/median, range, standard deviation) (age)
- Bone involved in the fracture
- Type of fracture treatment (i.e. operative, non-operative)

**Outcomes: Definitions and measures**
- Primary outcome (Non-union, defined as a delay to union > 6 months)
- Secondary outcome (Delayed union, defined as a delay to union >3 months, reoperation, pain scores)
- Adverse effects of treatment (description of outcome as reported)

**Outcomes: Results**
Data for all outcomes specified in the protocol will be entered in the following format:
- Outcome (description of outcome measure)
- Results for intervention (summary or ‘not stated’)

---