Clinician Survey – Delphi Study documents

1.1 Protocol clinician survey protocol

Systematic Review to Identify Important Outcomes for the Delphi Process Component of the DINOSAUR Study and Outline of Delphi Process

BACKGROUND

Osteomyelitis (OM) and septic arthritis (SA) are relatively uncommon infections in children. The exact incidence of these infections in the UK is not accurately known, however, it is estimated at 3 in 100000 per year in the UK (2001). [1] The DINOSAUR study is an NIHR HTA funded project, consisting of a service evaluation including forty-four NHS hospitals, a microbiology sub-study investigating the bacterial pathology using molecular techniques on samples from six tertiary hospitals, and a qualitative study and Delphi analysis to ascertain outcomes that are important to patients and clinicians when considering treatment of bone and joint infections in children. The DINOSAUR Study service evaluation will provide up-to-date epidemiological data for OM and SA in the UK. (www.dinosaur-study.org.uk).

There is no international and little UK consensus regarding the route or duration of antibiotic treatment of acute OM/SA in children, and one of the overall aims of the DINOSAUR study, including this Delphi process is to try to gain UK consensus and develop a national guideline if consensus is achieved.

Sequential intravenous (IV) and oral antibiotic therapy is commonly used, as this allows effective antibiotic delivery when the patient is unwell, and ongoing antibiotic therapy without the need for intravenous access once clinical improvement is seen. This may reduce hospital stay, cost and inconvenience; however, there is limited current evidence to aid the clinical decision of when to switch from IV to oral therapy, which can be applied to the UK population. .

A Canadian systematic review of short (≤7 days) versus long course (>7 days) IV antibiotic treatment for acute OM in children, due primarily to S. aureus, showed no difference in the overall cure rate after 6 months. [2] Similarly a retrospective cohort study of 1969 children in the US found that early switch to oral therapy (median 4 days) was as effective as prolonged IV treatment,[3] a finding also suggested in a smaller retrospective study of 186 children with SA.[4] The laboratory or clinical parameters that would determine the decision to switch to

oral therapy remain undefined. The suggested duration for IV antibiotic treatment ranges from 3 days to 6 weeks, resulting from several observational studies with relatively poor evidence levels. In the past, the overall duration of antibiotic treatment has been considered an important factor to improve outcome and reduce relapse. Several paediatric and orthopaedic texts recommend at least 4 to 6 weeks of treatment.

Most clinicians continue IV antibiotics until the child shows clinical improvement, is afebrile and able to tolerate appropriate oral medication. Observing a decrease in inflammatory markers is thought to be of value. Studies have shown that serum CRP level decreased more rapidly than ESR in children recovering from acute OM,[5, 6] and children with CRP raised were more likely to have symptoms or extensive radiographic abnormalities.[7] A recent Finnish clinical trial showed apparently good long term results and no treatment failures using CRP as the biological marker [6, 8].

The project was initiated and developed through NIHR clinical networks, bringing together members of the Medicines for Children Research Network Clinical Studies Groups in Allergy, Immunology and Infectious Diseases and General Paediatrics (both of which have integrated parent representation) with representatives from the UK paediatric orthopaedic association, the national paediatric microbiology group and paediatric radiologists. The DINOSAUR project as a whole is coordinated by the MCRN Clinical Trials Unit.

SELECTION OF OUTCOMES FOR USE IN CLINICAL STUDIES OF DURATION OF ANTIBIOTIC THERAPY FOR PAEDIATRIC BONE AND JOINT INFECTIONS

The DINOSAUR Study includes a systematic review of the literature to identify outcomes used by previous trials investigating duration of antibiotics in bone and joint infections in children. Ideally clinical trials should have defined outcomes that answer questions generated by the main hypotheses, for example that there is no difference between prolonged and shortened courses of antibiotic therapy. When we consider outcomes that may be used in studies of the duration of antibiotic treatment for these infections by looking at relevant literature, it appears that potential outcomes are variable. They include chronic infection, recurrence of infection, disability and deformity and disorders of growth, as well as biochemical and microbiological outcomes.

In usual clinical practice the outcome of treatment of bone and joint infections is usually cure, or complete clinical recovery. This may be defined as regaining function of the affected limb,

resolution of fever or normalisation of inflammatory markers and / or imaging. There is a lack of standardisation of clinical care recognised internationally, and it is common to treat children beyond the time of resolution of symptoms, theoretically to prevent recurrence of infection.

Heterogeneity between studies

This refers to differences in the way outcomes stated in the literature may be evaluated by individual researchers. For example, the time of follow-up to assess complications varied from three months to five years between studies. Additionally different clinical outcomes were considered, including persistent pain, pathological fracture and disability. This limits the extent to which patients included in one study can be compared with patients from another, because the outcomes may be too heterogeneous.

Outcome reporting bias

Research groups are more likely to select particular outcomes, particularly where there has been a significant or positive finding.[9] This may mean that important outcomes may be overlooked in a particular trial, and the team was mindful of this when reviewing articles. Outcomes reported implicitly in the methods and in the discussion were included, and outcomes where there was no significant finding.

Additionally outcomes not detailed in the selected papers, but which are deemed important by the study operational group, have also been included. The combination of including a core outcome set selected from these papers following a comprehensive literature search should reduce outcome reporting bias.

AIMS AND OBJECTIVES

The aim of this study is to develop a core outcome set to use in a future RCT into shortened duration of antibiotic therapy for paediatric bone and joint infections using a combination of systematic review of the literature, expert opinion and Delphi process.

Additionally the Delphi process will be used to canvas opinion from stakeholder groups what criteria are used to switch from intravenous to oral antibiotic treatment, and these would then be used to decide duration of intravenous versus oral treatment in a RCT if this were deemed feasible following the DINOSAUR study.

The outcomes that are important to parents and children with bone and joint infections will be explored in a parallel qualitative study using interviews conducted by an experienced qualitative researcher. The findings from this parallel study will then be presented to stakeholders participating in the Delphi survey prior to the final round of the survey.

Types of studies

Ideally systematic reviews, large RCTs, large cohort studies and case series would be included in the literature review, however, the research group recognises that there is a paucity of high quality data and that RCTs investigating duration of antibiotic treatment generally include small numbers of patients.

Types of intervention

Any study investigating duration of antibiotic therapy used for bone and joint infection, regardless of what antibiotic agent was used, or the duration of intravenous versus oral antibiotic therapy.

Types of participants

All children from birth to 16 years treated with systemic antibiotics for bone and joint infections, regardless of surgical intervention, co-morbidities or site affected.

Exclusion criteria

Studies investigating the use of surgically placed antibiotic beads or other local antibiotic treatment were excluded. Predominantly adult studies with small numbers of children included were also excluded because the criteria for adult treatment is not the same as for paediatric cases as there are not the same risks of disability and deformity.

SEARCH STRATEGY – see Appendix 1 main report

ELIGIBILITY OF STUDIES

Of the 1321 papers identified, 218 were reviewed in detail. The remainder were excluded based on review of title, and where necessary abstract.

Of the 218 papers that were reviewed in detail 208 were excluded. Many were review articles discussing the existing literature, with no clear focus on intervention or outcome. All of the papers used in these articles were included in the original search. Articles comparing imaging

techniques and surgical techniques were also excluded as the outcomes were not relevant to our study investigating antibiotic duration.

Two systematic reviews were selected, and the papers used analysed in detail. Le Saux et al2002 and found 12 prospective studies including one RCT comparing duration of antibiotics for acute haematogenous osteomyelitis. [10]The numbers of patients included in these studies was small, in some cases fewer than ten, however, overall the conclusion was that there is no difference in outcome between long and short courses of antibiotic treatment.

Of the papers used in this systematic review three were selected for this analysis. The remainder did not have clearly stated outcomes or follow-up for patients.

Howard-Jones et al also published a systematic review of treatment of sub-acute and chronic pyogenic osteomyelitis in 2010. This review looked at studies comparing both duration of antibiotic treatment, and studies comparing different antibiotic agents. Of the papers used in this analysis, five were selected by the reviewers. Two of these had also been included in the Le Saux study. One study was excluded because it predominantly included children with cellulitis and soft tissue infection and therefore outcomes therefore would not be comparable to a group with bone and joint infections only. The other excluded papers did not clearly state the outcome measures used to define 'cure'.

All of the studies reviewed in detail and selected for use in this Delphi study are detailed below. We used the following criteria for assessing papers and identifying outcomes:

1. Is the primary outcome clearly stated?

2. Is the primary outcome clearly defined so that another researcher would be able to reproduce its measurement?

3. Are any secondary outcomes clearly stated, and defined?

4. Do the authors explain the use of the outcomes they have selected?

EXTRACTION OF DATA

Data was extracted from each of the papers by a single reviewer (PS) and checked by a second (SF). These outcomes were then discussed with a study advisory group, who also had the opportunity to review the papers and consensus was gained that all of the available outcomes had been extracted.

All of the papers are exclusively paediatric. The following data was extracted in the first instance: Authors, journal and year of publication, type of study, number of cases included in the study and exclusion criteria. This is detailed in table 2 (see Appendix 1 main report) below.

The key outcomes are combined and summarised below. These were then discussed with the study advisory group, including paediatric infectious disease consultants, orthopaedic surgeons general paediatricians, and radiologists. Following this discussion the important outcomes for a potential future RCT were identified. These are summarised in table 3 (see Appendix 1 main report).

Outcomes Important to Patients

Outcomes that are important to parents and patients will be identified by a parallel qualitative study in which thirty patients will be interviewed by a trained qualitative researcher. The experiences of these patients' treatment and hospital admission will be explored, as well as their understanding of their illness, and willingness to participate in a future RCT. The findings of this qualitative study will be presented to stakeholders either in a third round of Delphi survey, or at a meeting including members of all stakeholder groups including parents.

Outcomes Important to Clinical Stakeholders:Participants

The final core outcome set and criteria for IV to oral antibiotic switch will be ascertained using 2 rounds of Delphi process to gain consensus from all clinical stakeholders on which outcomes are most relevant to a future RCT. In the first round all stakeholders (i.e. paediatricians, orthopaedic surgeons, paediatric infectious disease specialists, paediatric microbiologists, paediatric radiologists) will be approached by email containing a link to the DINOSAUR study. These stakeholders will be identified using mailing lists from the British Paediatric Allergy, Immunology and Infection Group (BPAIIG), Royal College of Paediatrics and Child Health (RCPCH), British Society for Children's Orthopaedic Surgery (BSCOS),British Society or Paediatric Radiology (BSPR) and the British Society for Antimicrobial Chemotherapy (BSAC) , and are anticipated to be from all secondary and tertiary hospitals within the UK.

Only individuals who have treated a child with septic arthritis or osteomyelitis in the last 12 months will be asked to participate. Many but not all of these individuals will already be

principle investigators for the DINOSAUR study at their local site. The Delphi process will not be limited to sites participating in the service evaluation, however, as it is our aim to obtain a wide range of clinical opinions.

At the beginning of the process all participants will be reminded of the importance of completing three rounds of the Delphi process. Many will be motivated by the potential to shape the future RCT, but if there is poor initial response, the stake holder groups will be sent reminder emails, each with a link to the DINOSAUR Delphi study. Once they have clicked on the link they will asked to create a unique account linking to the study, allowing them to participate in all three rounds.

DELPHI ROUND 1

In the first round the online questionnaire will request the participant's name and email address together with their clinical role and hospital where they work. This information will be stored in a separate database and used to provide the respondent with a unique identifier. A unique identifier will allow identification of individuals completing all rounds of the Delphi exercise.

Participants will be asked to complete each round of the Delphi exercise within 3 weeks of receipt of the email and will be reminded of this at the start of each survey. A reminder email will be send at the end of week 2 to prompt completion of the survey.

Round 1 survey format

The survey was presented in an online format (see questionnaire in this document).

Round 1 content includes: the respondent's clinical role; a list of outcomes to be scored, ordered alphabetically; and an option for a participant to add any additional outcomes and comments and to provide a score for each outcome added.

At the beginning of the survey, participants will be presented with the information from the DINOSAUR study service evaluation in which 44 centres prospectively collected clinical data for all children admitted with bone and joint infections for a six month period. They will be asked the key questions:

'What outcomes influence your decision to switch from intravenous to oral antibiotics when treating a child with osteoarticular infection?'

‘What outcomes influence the total duration of antibiotics when treating a child with osteoarticular infection?’

‘What line or treatment related complications are important when using prolonged courses of antibiotics?’

Participants will be asked to score each of the outcomes listed using the Grading of Recommendations, Assessment, Development and Evaluations scale of 1 to 9. In the Delphi exercise the scale will be presented in the format 1 to 9, with 1to 3 labelled ‘not important’, 4 to 6 labelled ‘important but not critical’ and 7 to 9 labelled ‘critical’ . Participants will be provided with an option to add additional outcomes that they think are relevant together with a score for each outcome added.

Outcomes will be listed alphabetically to avoid potential weighting of outcomes caused by the order in which they are displayed.

Analysis of Round 1

The study advisory group, consisting of members from all stakeholder groups will review any outcomes added to the list during round one and assess whether these differ significantly from those already on the list. If they are deemed to be important outcomes that have not yet been identified they will be categorised .

For each outcome, the number of participants who have scored the outcome and the distribution of scores (as percentage who have scored each outcome) will be summarised by stakeholder group. All outcomes will be carried forward to round 2.

Response rate in round 1

The number of participants in each stakeholder group who respond to round 1 will be assessed following round 1 closure. Results will be presented as: the total number of registrations; a breakdown of respondents who have completed the survey and their inclusion in the initial email invitation; the total number of respondents who completed the round; the total number of respondents in each stakeholder group; the percentage of respondents compared with potential respondents as identified from the information provided by clinical leads; and the percentage of respondents from other sources (not included in original email invitation).

Continuation to round 2 will be considered based on the response to round 1. If a low number of responders (<10) is observed for one or more stakeholder groups, the Delphi protocol for future rounds will be reviewed and revised. Where there is only one stakeholder group with a small number of respondents (potentially due to the sample available from clinical teams) then consideration will be given to grouping with another stakeholder group. This will be done in consultation with the study advisory group to ensure appropriateness of grouping.

The following proposed approach for round 2 assumes sufficient numbers of stakeholders from each group respond.

DELPHI ROUND 2

Round two will also be presented online. Each participant will be presented with their individual scores from round 1 together with the number of respondents and distribution of scores for each outcome for their particular stakeholder group. They will then be asked to score the outcomes again. Additionally in round two they will be asked if they are willing to participate in a RCT in future. This will be an open question allowing participants to give comments on what reservations they would have regarding a RCT.

DELPHI ROUND 3 AND CONSENSUS MEETING

This will depend on the response rate of round 2 (as described in round 1). At this stage the results of the interviews with patients and parents regarding their experiences of treatment, outcomes of importance and willingness to participate in a RCT will be include. Participants will then be asked to rescore all outcomes and state whether they should be included in a core outcome set.

The total number of participants invited to take part in round 3 will be recorded. For each outcome, the number of participants who have scored the outcome and the distribution of scores will be summarised together with the number of participants who have scored the outcome in all rounds. Results of the stakeholder group response will be compared with the whole group response and the percentage agreement used to determine the structure and focus of the final consensus meeting, which may be done as part of round 3. Each outcome will be classified as ‘consensus in’, ‘consensus out’ or ‘no consensus’ depending on scores.

The core outcome set can then be openly discussed by participants from each stakeholder group. The feasibility of doing a RCT of shortened duration of antibiotic therapy for

paediatric bone and joint infections can be assessed, and a core outcome set, and IV to oral switch criteria will have been determined by this process if a RCT is deemed feasible. If it is deemed that a RCT is not feasible the results of this Delphi survey may be used to develop a guideline for the treatment of bone and joint infections in children.

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1.2 Questionnaire Round 1 and 2

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Version 1.0

DINOSAUR Consensus Meeting

27th April 2015

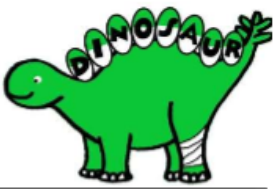
Delphi Questionnaire Scoring Sheet

Please answer each question by using the scoring system provided. If you feel you do not have the clinical expertise to answer a particular question please select 'unable to score'.

Part 1 – What criteria are important to you when deciding when or whether to switch from intravenous to oral antibiotic therapy?

Outcome	Importance									Unable to score
	Not important			Important but not critical			Critical			
	1	2	3	4	5	6	7	8	9	
CRP <20										
CRP less than one third of the presenting value										
CRP less than two thirds of the presenting value										
ESR <20										
Resolution of fever for 48h or more										
Weight bearing / return of function to limb										
Resolution of pain										
Tolerating oral input										
Parental opinion regarding improvement or worsening of condition										
Pain improvement (rather than resolution)										

NB: These oral switch criteria relate ONLY to uncomplicated unifocal osteomyelitis or septic arthritis in a previously healthy child. We are not referring to immunocompromised children or those in whom resistant organisms are isolated or clinically suspected.

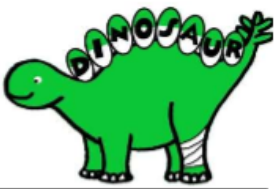


Part 2– What outcomes should be measured to assess whether treatment has been effective?

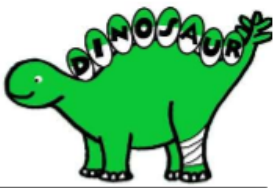
A. Infection related (consider for primary and secondary outcomes)

Outcome	Importance									Unable to score
	Not important			Important but not critical			Critical			
	1	2	3	4	5	6	7	8	9	
Need for non-diagnostic surgical procedure (e.g. decompression, debridement)										
Re-hospitalisation or recurrence of symptoms while on oral antibiotics										
Treatment failure – recurrence of infection (either at original site or at new site)										
Pain while on antimicrobial treatment										
Ongoing pain at follow-up										
Disability at follow-up										
Symptom free at 1 year										
Limb shortening or deformity										
Duration to CRP <5										
Duration to resolution of fever										
Duration to resolution of pain										
Duration of hospital stay										
Fracture at or near site of infection										
Prolonged antibiotic therapy										
Quality of life										

B. Infection related (rarer events to consider need to capture in a clinical trial)										
Outcome	Importance									Unable to score
	Not important			Important but not critical			Critical			
	1	2	3	4	5	6	7	8	9	
Chronic osteomyelitis										
Chronic arthritis										
Chronic myositis										
Amputation or Fasciotomy										
Death										
PICU requirement (e.g. PICU-free days at day 30, if admitted)										



C. Treatment / Line Related										
Outcome	Importance									Unable to score
	Not important			Important but not critical			Critical			
	1	2	3	4	5	6	7	8	9	
Agranulocytosis / neutropaenia										
Deranged liver function										
Clostridium difficile infection										
Rash or allergic reaction										
Suspected drug-related fever										
Line infection										
Line occlusion										
Vomiting / diarrhoea										
IV antibiotic necessitated insertion of PICC or other central line										
Infiltration or extravasation event										
Any complication of vascular access										



Part 3 - Assuming agreement can be reached regarding criteria for switching and the outcomes that will be used to compare treatment approaches, would you be willing to recruit patients to a national randomised controlled trial investigating prolonged versus short courses of antibiotic treatment for simple acute osteomyelitis and septic arthritis in previously healthy children?			
	Yes		No
Free text comments (if any):			

1.3 Consensus meeting agenda

Duration of **IN**travenous antibi**O**tic therapy for **S**eptic **A**rthritis or ac**U**te osteomyelitis in a paediat**R**ic population

Agenda

09:30 Arrival and registration

- 09:45-10:15 *Parallel session for parents and young people only*

10:15 Welcome & Introduction to the DINOSAUR Study

Aims of today:

1. **How feasible is a future trial and what should the design be?**
2. **What should the switching criteria be?**
3. **What are the core outcomes?**

- Sources of information/methods – service evaluation, qualitative interviews/Delphi

10:30 How feasible is a future trial?

- Results from service evaluation
- Results from qualitative interviews
- Potential trial design: do the results indicate a trial of reduced length antibiotics with an IV to oral switch according to predefined criteria in previously well children with bone and joint infection will be possible?

11:45 What should the switching criteria be?

- Results from the service evaluation
- Results from qualitative interviews
- Results from the Delphi
- Discussion and Voting

12:45 Lunch

***13:15* What are the core outcomes?**

- Results from qualitative interviews
- Results from the Delphi
- Discussion and Voting

14.45 Summary

- Discussion about proposed trial design, outcomes. switching criteria and overall feasibility

16:00 Meeting close